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(54) Title: METHODS OF DETERMINING CANCER PROGNOSIS VIA NATURAL KILLER CELL ACTIVITY

(57) Abstract: A method of determining a prognosis for a subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70) includes the step of comparing natural killer (NK) cell activity in a test sample with NK cell activity in a control sample. The control sample can be taken from the subject before dosing with the agent and the test sample can be taken from the subject after dosing with the agent. An increase in NK cell activity in the test sample compared with the control sample can indicate an improved prognosis.

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AP2

METHODS OF DETERMINING CANCER PROGNOSIS VIA NATURAL KILLER CELL ACTIVITY

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/671,833, filed on April 15, 2005. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Various therapies are known for cancer, for example, combination therapies of bis(thiohydrazide amides) and taxanes have described in U.S. Patent Nos. 6,800,660, 6,762,204, U.S. Pat. Appl. Ser. Nos. 10/345,885 filed January 15, 2003, and 10/758,589, January 15, 2004, the entire teachings of which are incorporated herein by reference. While such therapies can be effective, there exists a continuing need in the art for methods of improving treatments.

SUMMARY OF THE INVENTION

In various embodiments, a method of determining a prognosis for a subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70) includes the step of comparing natural killer (NK) cell activity in a test sample with NK cell activity in a control sample. The control sample can be taken from the subject before dosing with the agent and the test sample can be taken from the subject after dosing with the agent. An increase in NK cell activity in the test sample compared with the control sample can indicate an improved prognosis.

In various embodiments, a method for optimizing dosing for a subject undergoing cancer therapy, wherein the dosing includes administration of an agent that activates heat shock protein 70 (Hsp70) and an anticancer agent that is a microtubule stabilizer (e.g., taxane) includes the steps of:

a. changing dosing of the agent and/or the taxane during therapy;

b. comparing natural killer (NK) cell activity in a control sample with NK cell activity in a test sample;

c. comparing side effects from the agent and/or taxane between the test sample and the control sample;

d. optimizing dosing of the agent and/or taxane based on the dosing in step a) in combination with the results of step b) or step c).

As above, the test sample is taken from the subject after changing the dosing; and the control sample is taken from the subject before changing the dosing.

In various embodiments, a method for optimizing dosing for a subject undergoing cancer therapy with a bis(thio-hydrazide) amide and a taxane includes the steps of:

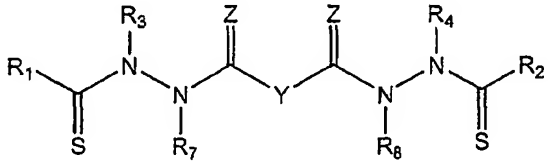
a. changing dosing of the bis(thio-hydrazide) amide and/or taxane during the cancer therapy;

b. comparing Hsp70 activity in a control sample with Hsp70 activity in a test sample;

c. comparing side effects from the bis(thio-hydrazide) amide and/or taxane at the time of the control sample with side effects from the bis(thio-hydrazide) amide and/or taxane at the time of the test sample;

d. optimizing dosing of the bis(thio-hydrazide) amide based on the dosing in step a) in combination with the results of steps b) and c).

The bis(thio-hydrazide) amide can be represented by the following Structural Formula:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

As above, the test sample can be taken from the subject after changing the dosing; and the control sample is taken from the subject before changing the dosing.

In some embodiments, a method of determining a prognosis for at least one subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70), include the step of comparing Hsp70 levels in the test sample with Hsp70 levels in the control sample. An increase in Hsp70 levels in the test sample compared with the control sample can indicate an improved prognosis. In certain embodiments, the dosage can be changed to maximize the Hsp70 levels for at least a portion of the treatment, which can improve the subject's prognosis compared to lower Hsp70 levels.

In some embodiments, a method of dosing a subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70) includes administering to the subject a predicted dose based on a data analysis for a representative population (e.g., a population of test subjects with cancer), the data comprising natural killer (NK) cell activity, agent dosing, and therapeutic result. The data can be collected as described above.

In some embodiments, a method of dosing a subject undergoing cancer therapy, wherein the dosing includes administration of an agent that activates heat shock protein 70 (Hsp70) and a taxane includes administering to the subject a predicted dose based on data analysis of a representative population, the data comprising natural killer (NK) cell activity, agent/taxane dosing, and therapeutic result. The data can be collected as described above.

The methods are believed to be useful for optimizing dosing for particular subjects, and also for optimizing predicted dosing for subjects based on testing and analysis of representative subject populations with cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

FIGs 1A, 1B, and 1C are bar graphs showing the percent increase in Hsp70 plasma levels associated with administration of the Compound (1)/paclitaxel combination therapy at 1 hour (FIG 1A), 5 hours (FIG 1B), and 8 hours (FIG 1C) after administration.

FIG 2 is a Kaplan-Meier graph of time-to-progression (resumption of cancer growth) in studies of various combinations of platinum anticancer drugs and taxanes. Also shown is the disclosed combination of a bisthiohydrazide (Compound (1)), a taxane (paclitaxel) and also a platinum anticancer drug, carboplatin. The preliminary data in show that the disclosed method is superior to the platin/taxane combination alone.

DETAILED DESCRIPTION OF THE INVENTION

A description of preferred embodiments of the invention follows.

In various embodiments, a method of determining a prognosis for a subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70), includes the step of comparing natural killer (NK) cell activity in a test sample with NK cell activity in a control sample. The control sample is taken from the subject before dosing with the agent, the test sample is taken from the subject after dosing with the agent. An increase in NK cell activity in the test sample compared with the control sample is indicative of an improved prognosis.

In various embodiments, the test sample can be taken from the subject within from about 1 hour to about 90 days after being administered the agent, e.g., a bis(thio-hydrazide) amide. In some embodiments, the test sample is taken from the subject at about 7 days after being administered a second dose of the bis(thio-hydrazide) amide. In certain embodiments, the test sample is taken from the subject at about 28 days after being administered the bis(thio-hydrazide) amide.

In some embodiments, the prognosis can be determined for a single subject. In certain embodiments, for each of a plurality of subjects in a population, data can be collected for comparative NK cell activity between samples, dosing, and therapeutic result. Also included is analyzing the data for the population to predict a dose to achieve an improved prognosis in a subject that is representative of the subject population. Typically, the subjects can be human.

In various embodiments, the NK cell activity in the control sample and the test sample can be assessed by contacting each sample with target cells, and assessing a death rate for the target cells, wherein the target cell death rate corresponds to the NK cell activity. In some embodiments, the NK cell activity can be assessed in one or more peripheral blood mononuclear cell (PBMC) samples isolated from the subject's blood. In some embodiments, the NK cell activity can be assessed in a sample taken from a tumor in the subject.

The subject can have any cancer as defined herein. In various embodiments, the subject can have a cancer selected from fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia; chronic leukemia; and polycythemia vera, lymphoma, multiple myeloma, Waldenstrobm's macroglobulinemia, and heavy chain disease. In particular embodiments, the subject can have a cancer selected

from metastatic melanoma, non-small lung cell carcinoma, or a soft tissue sarcoma. As used herein, "soft-tissue sarcomas" (STS) are cancers that begin in the soft tissues that support, connect, and surround various parts of the body for example, soft tissues such as muscles, fat, tendons, nerves, and blood vessels, lymph nodes, or the like. Such STSs can occur anywhere in the body, though typically about one half occur in the limbs. In various embodiments, STSs can include one or more cancers selected from liposarcoma, fibrosarcoma, malignant fibrous histiocytoma leiomyosarcoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, or the like.

In various embodiments, the agent, e.g., a bis(thio-hydrazide) amide can be co-administered with a taxane. In some embodiments, the bis(thio-hydrazide) amide is co-administered with paclitaxel.

In various embodiments, the agent, e.g., the bis(thio-hydrazide) amide can be co-administered with a platinum anticancer compound. The platinum anticancer compound can be cisplatin; carboplatin; dexormaplatin; enloplatin; iproplatin; lobaplatin ; lomnedaplatin; ormaplatin; oxaliplatin; spiroplatin; or zeniplatin. In particular embodiments, the platinum anticancer compound can be carboplatin.

In various embodiments, a method for optimizing dosing for a subject undergoing cancer therapy, wherein the dosing includes administration of an agent that activates heat shock protein 70 (Hsp70) and a taxane, includes the steps of:

a. changing dosing of the agent and/or the taxane during therapy;

b. comparing natural killer (NK) cell activity in a control sample with NK cell activity in a test sample;

c. comparing side effects from the agent and/or taxane between the test sample and the control sample;

d. optimizing dosing of the agent and/or taxane based on the dosing in step a) in combination with the results of step b) or step c).

As above, the test sample is taken from the subject after changing the dosing; and the control sample is taken from the subject before changing the dosing.

In various embodiments, the dosing is optimized for a single subject. In some embodiments, steps a)-c) can be performed for a plurality of subjects in a population

of subjects with cancer. Step d) further includes analyzing the collected results from steps a)-c) and determining a representative optimized dose based on the subject population, e.g., a population of subjects with cancer.

In some embodiments, the method also includes repeating steps a)-c).

In various embodiments, a method for optimizing dosing for a subject undergoing cancer therapy with a bis(thio-hydrazide) amide and a taxane includes the steps of:

a. changing dosing of the bis(thio-hydrazide) amide and/or taxane during the cancer therapy;

b. comparing Hsp70 activity in a control sample with Hsp70 activity in a test sample;

c. comparing side effects from the bis(thio-hydrazide) amide and/or taxane at the time of the control sample with side effects from the bis(thio-hydrazide) amide and/or taxane at the time of the test sample;

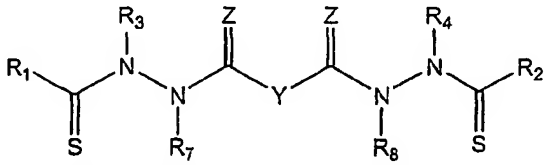
d. optimizing dosing of the bis(thio-hydrazide) amide based on the dosing in step a) in combination with the results of steps b) and c).

As above, the test sample can be taken from the subject after changing the dosing; and the control sample is taken from the subject before changing the dosing.

In various embodiments, steps a)-c) can be repeated. In various embodiments, Hsp70 activity is compared between samples by contacting each sample with an enzyme linked immunosorbent assay specific for Hsp70.

In various embodiments, the test sample (e.g., the Hsp70 activity sample) is taken from the subject from about 1 to about 48 hours after dosing, in some embodiments, from about 5 to about 24 hours after dosing, or in particular embodiments, about 8 hours after dosing.

In various embodiments, the bis(thio-hydrazide) amide can be represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

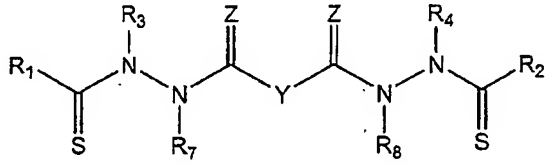
In some embodiments, a method of determining a prognosis for at least one subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70), include the step of comparing Hsp70 levels in the test sample with Hsp70 levels in the control sample. An increase in Hsp70 levels in the test sample compared with the control sample can indicate an improved prognosis. In certain embodiments, the dosage can be changed to maximize the Hsp70 levels for at least a portion of the treatment, which can improve the subject's prognosis compared to lower Hsp70 levels.

In some embodiments, a method of dosing a subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70) includes administering to the subject a predicted dose based on a data analysis for a representative population (e.g., a population of test subjects with cancer), the data comprising natural killer (NK) cell activity, agent dosing, and therapeutic result. The data can be collected as described above.

In some embodiments, a method of dosing a subject undergoing cancer therapy, wherein the dosing includes administration of an agent that activates heat shock protein 70 (Hsp70) and a taxane includes administering to the subject a predicted dose based on data analysis of a representative population, the data comprising natural killer (NK) cell activity, agent/taxane dosing, and therapeutic result. The data can be collected as described above.

A method for dosing at least one subject undergoing cancer therapy with a bis(thio-hydrazide) amide and a taxane, wherein the bis(thio-hydrazide) amide is represented by Structural Formula I includes administering to the subject a predicted dose based on data analysis of a representative population, the data comprising heat shock protein 70 (Hsp70) levels, bis(thio-hydrazide) amide/taxane dosing, and therapeutic result. The data can be collected as described above.

The agent that activates heat shock protein 70 (Hsp70) can be a the bis(thio-hydrazide) amide, e.g., as represented by Structural Formula I.



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

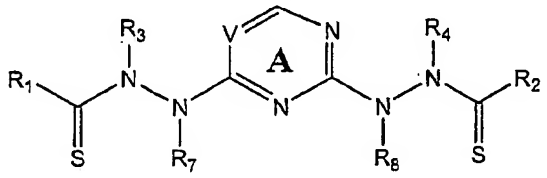
R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

In one embodiment, Y in Structural Formula I is a covalent bond, -C(R_5R_6)-, -(CH_2CH_2)-, trans-(CH=CH)-, cis-(CH=CH)- or –(C ≡C)- group, preferably -C(R_5R_6)-. R_1-R_4 are as described above for Structural Formula I. R_5 and R_6 are each independently -H, an aliphatic or substituted aliphatic group, or R_5 is -H and R_6 is an optionally substituted aryl group, or, R_5 and R_6, taken together, are an optionally substituted C2-C6 alkylene group. The pharmaceutically acceptable cation is as described in detail below.

In specific embodiments, Y taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group. In this instance, certain bis(thiohydrazide amides) are represented by Structural Formula II:

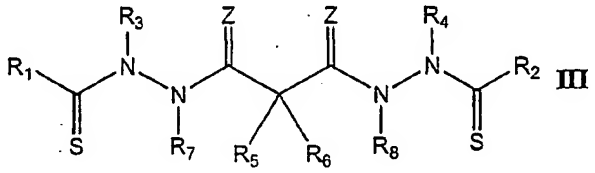


II

;

wherein Ring A is substituted or unsubstituted and V is –CH- or –N-. The other variables in Structural Formula II are as described herein for Structural Formula I or III.

In particular embodiments, the bis(thiohydrazide amides) are represented by Structural Formula III:



III

R_1-R_8 and the pharmaceutically acceptable cation are as described above for Structural Formula I.

In Structural Formulas I-III, R_1 and R_2 are the same or different and/or R_3 and R_4 are the same or different; preferably, R_1 and R_2 are the same and R_3 and R_4 are the same. In Structural Formulas I and III, Z is preferably O. Typically in Structural Formulas I and III, Z is O; R_1 and R_2 are the same; and R_3 and R_4 are the same. More preferably, Z is O; R_1 and R_2 are the same; R_3 and R_4 are the same, and R_7 and R_8 are the same.

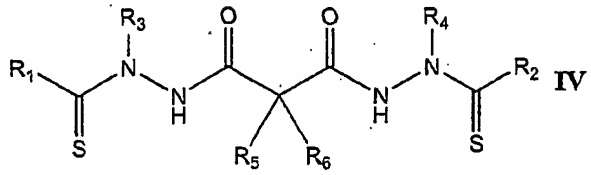
In other embodiments, the bis(thiohydrazide amides) are represented by Structural Formula III: R_1 and R_2 are each an optionally substituted aryl group, preferably an optionally substituted phenyl group; R_3 and R_4 are each an optionally substituted aliphatic group, preferably an alkyl group, more preferably, methyl or ethyl; and R_5 and R_6 are as described above, but R_5 is preferably –H and R_6 is preferably –H, an aliphatic or substituted aliphatic group.

Alternatively, R_1 and R_2 are each an optionally substituted aryl group; R_3 and R_4 are each an optionally substituted aliphatic group; R_5 is -H; and R_6 is -H, an aliphatic or substituted aliphatic group. Preferably, R_1 and R_2 are each an optionally substituted aryl group; R_3 and R_4 are each an alkyl group; and R_5 is -H and R_6 is -H or methyl. Even more preferably, R_1 and R_2 are each an optionally substituted phenyl group; R_3 and R_4 are each methyl or ethyl; and R_5 is -H and R_6 is -H or methyl. Suitable substituents for an aryl group represented by R_1 and R_2 and an aliphatic group represented by R_3, R_4 and R_6 are as described below for aryl and aliphatic groups.

In another embodiment, the bis(thiohydrazide amides) are represented by Structural Formula **III**: R_1 and R_2 are each an optionally substituted aliphatic group, preferably a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group, more preferably cyclopropyl or 1-methylcyclopropyl; R_3 and R_4 are as described above for Structural Formula **I**, preferably both an optionally substituted alkyl group; and R_5 and R_6 are as described above, but R_5 is preferably –H and R_6 is preferably –H, an aliphatic or substituted aliphatic group, more preferably –H or methyl.

Alternatively, the bis(thiohydrazide amides) are represented by Structural Formula **III**: R_1 and R_2 are each an optionally substituted aliphatic group; R_3 and R_4 are as described above for Structural Formula **I**, preferably both an optionally substituted alkyl group; and R_5 is –H and R_6 is –H or an optionally substituted aliphatic group. Preferably, R_1 and R_2 are both a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group; R_3 and R_4 are both as described above for Structural Formula **I**, preferably an alkyl group; and R_5 is –H and R_6 is –H or an aliphatic or substituted aliphatic group. More preferably, R_1 and R_2 are both a C3-C8 cycloalkyl group optionally substituted with at least one alkyl group; R_3 and R_4 are both an alkyl group; and R_5 is –H and R_6 is –H or methyl. Even more preferably, R_1 and R_2 are both cyclopropyl or 1-methylcyclopropyl; R_3 and R_4 are both an alkyl group, preferably methyl or ethyl; and R_5 is –H and R_6 is –H or methyl.

In specific embodiments, the bis(thiohydrazide amides) are represented by Structural Formula IV:

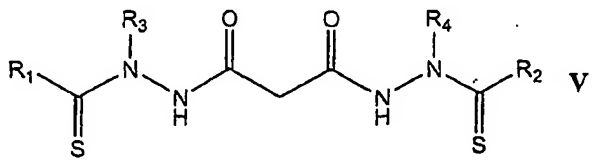


IV

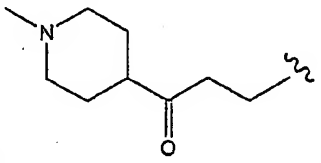
wherein: R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 4-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both ethyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 4-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 3-cyanophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 3-fluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 4-chlorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 3-methoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,3-dimethoxyphenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-difluorophenyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 2,5-dichlorophenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethylphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both phenyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2,5-dimethoxyphenyl, R_3 and

R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is methyl and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is ethyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, R_5 is *n*-propyl, and R_6 is -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both methyl; R_1 and R_2 are both 1-methylcyclopropyl, R_3 and R_4 are both ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-methylcyclopropyl, R_3 is methyl, R_4 is ethyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2-methylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 2-phenylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both 1-phenylcyclopropyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclobutyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclopentyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both cyclohexyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both *t*-butyl, and R_5 and R_6 are both -H; R_1 and R_2 are both methyl, R_3 and R_4 are both phenyl, and R_5 and R_6 are both -H; R_1 and R_2 are both *t*-butyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; R_1 and R_2 are ethyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H; or R_1 and R_2 are both *n*-propyl, R_3 and R_4 are both methyl, and R_5 and R_6 are both -H.

In specific embodiments, the bis(thiohydrazide amides) are represented by Structural Formula V:



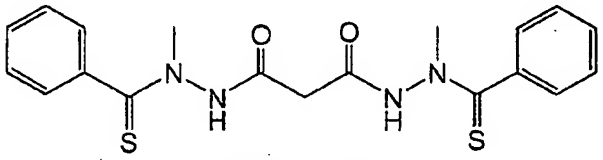
V

wherein: R_1 and R_2 are both phenyl, and R_3 and R_4 are both *o*-CH_3-phenyl; R_1 and R_2 are both *o*-$CH_3C(O)O$-phenyl, and R_3 and R_4 are phenyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both *n*-propyl; R_1 and R_2 are both *p*-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both *p*-nitro phenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both *n*-butyl; R_1 and R_2 are both *p*-chlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-nitrophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-cyanophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-fluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-furanyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both 2-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3-methoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,3-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both 2,5-difluorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dichlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2,5-dimethylphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methoxy-5-chlorophenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 3,6-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both phenyl, and R_3 and R_4 are both 2-ethylphenyl; R_1 and R_2 are both 2-methyl-5-pyridyl, and R_3 and R_4 are both methyl; or R_1 is phenyl; R_2 is 2,5-dimethoxyphenyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *p*-CF_3-phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *o*-CH_3-phenyl; R_1 and R_2 are both $-(CH_2)_3COOH$; and R_3 and R_4 are both phenyl; R_1 and R_2 are both represented by the following structural formula: 

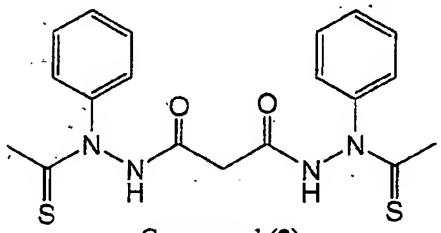
,and R_3 and R_4 are both phenyl; R_1 and R_2 are both *n*-butyl, and R_3 and R_4 are both phenyl; R_1 and R_2 are both *n*-pentyl, R_3 and R_4 are both phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2-pyridyl; R_1 and R_2 are both cyclohexyl, and R_3 and R_4 are

both phenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2-ethylphenyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both 2,6-dichlorophenyl; R_1-R_4 are all methyl; R_1 and R_2 are both methyl, and R_3 and R_4 are both *t*-butyl; R_1 and R_2 are both ethyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both *t*-butyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopropyl, and R_3 and R_4 are both ethyl; R_1 and R_2 are both 1-methylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-methylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 1-phenylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both 2-phenylcyclopropyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclobutyl, and R_3 and R_4 are both methyl; R_1 and R_2 are both cyclopentyl, and R_3 and R_4 are both methyl; R_1 is cyclopropyl, R_2 is phenyl, and R_3 and R_4 are both methyl.

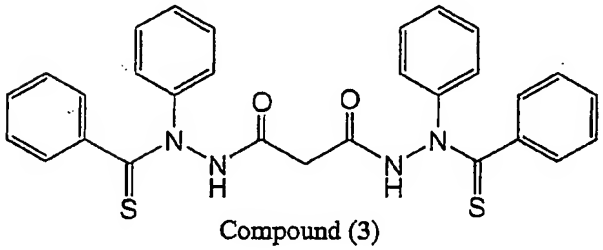
Preferred examples of bis(thiohydrazide amides) include Compounds (1)-(18) and pharmaceutically acceptable salts and solvates thereof:



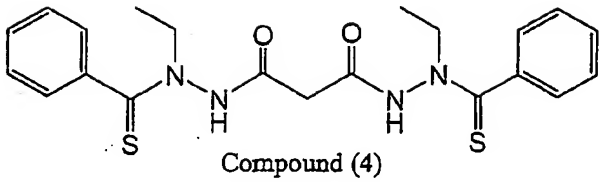
Compound (1) ;



Compound (2) ;

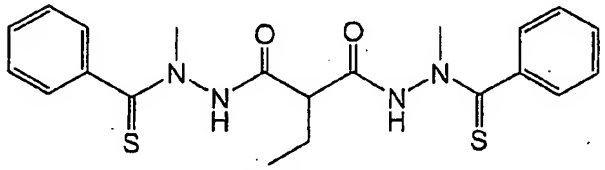


Compound (3) ;



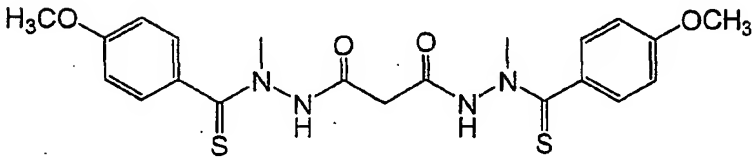
Compound (4)

;



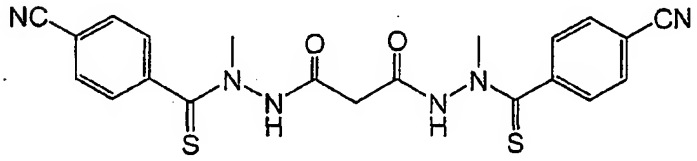
Compound (5)

;



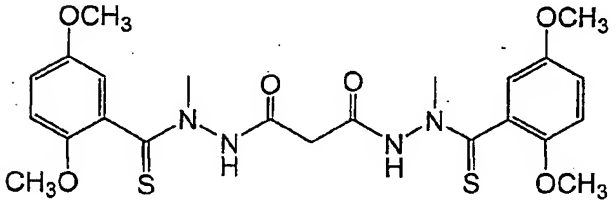
Compound (6)

;



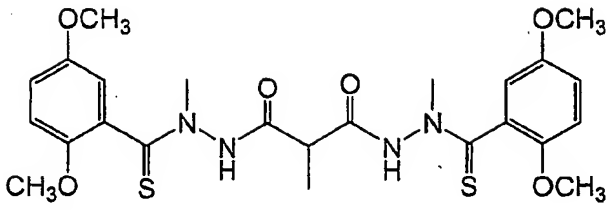
Compound (7)

;



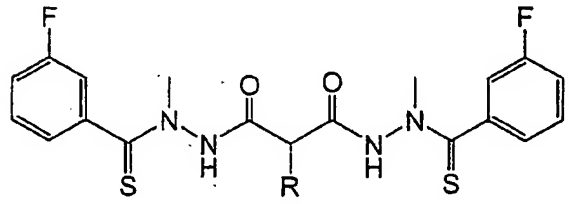
Compound (8)

;



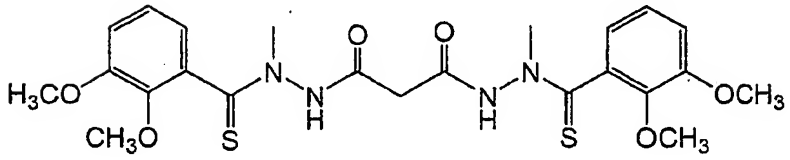
Compound (9)

;



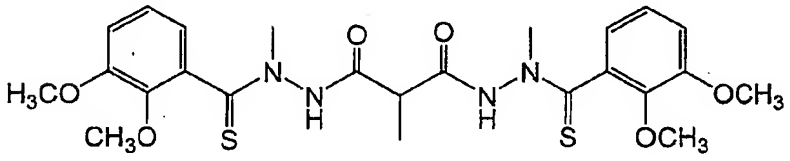
Compound (10)

;



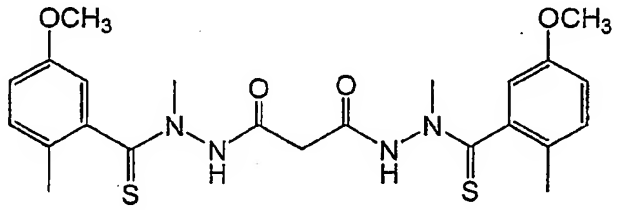
Compound (11)

;



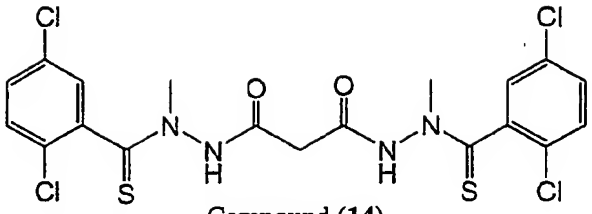
Compound (12)

;

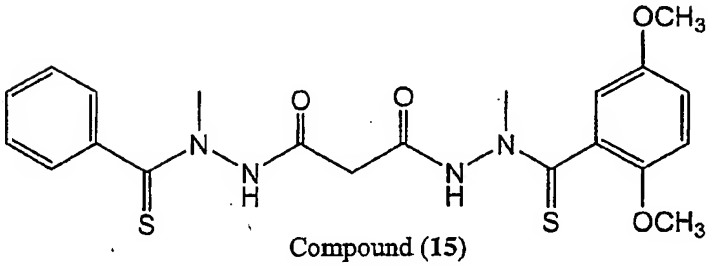


Compound (13)

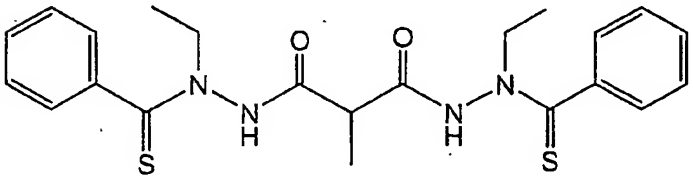
;



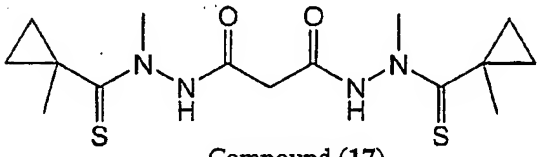
Compound (**14**) ;



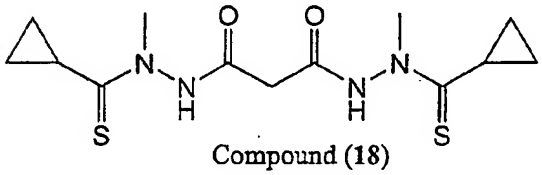
Compound (**15**) ;



Compound (**16**) ;



Compound (**17**) ; and

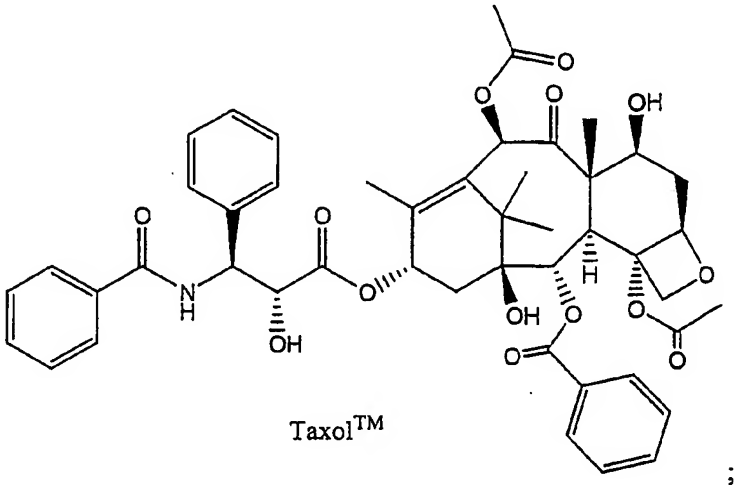


Compound (**18**)

Particular examples of bis(thiohydrazide amides) include Compounds (**1**), (**17**), and (**18**) and pharmaceutically acceptable salts and solvates thereof.

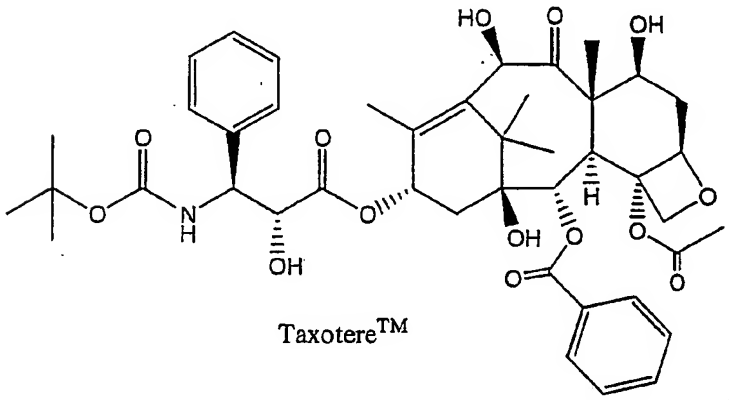
The taxanes employed employed in the disclosed invention include Taxol™ and Taxol™ analogs. Taxol™ or "paclitaxel" is a well-known anti-cancer drug which can act by enhancing and stabilizing microtubule formation. Thus, the term "Taxol™ analog" is defined herein to mean a compound which has the basic

Taxol™ skeleton and which stabilizes microtubule formation. Many analogs of Taxol™ are known, including Taxotere™, also referred to as "docetaxol". Taxol™ and Taxotere™ have the respective structural formulas:



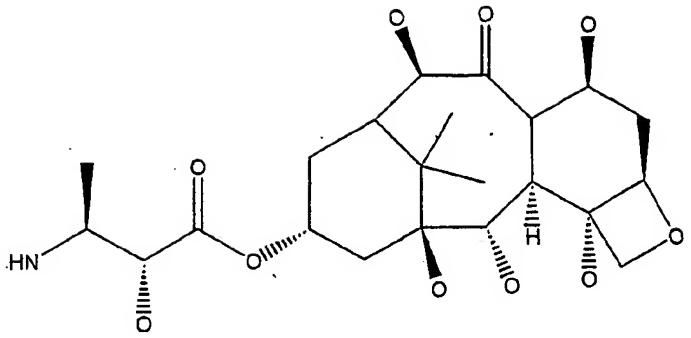
Taxol™

; and



Taxotere™

The taxanes employed in the disclosed invention have the basic taxane skeleton as a common structure feature shown below in Structural Formula VI:

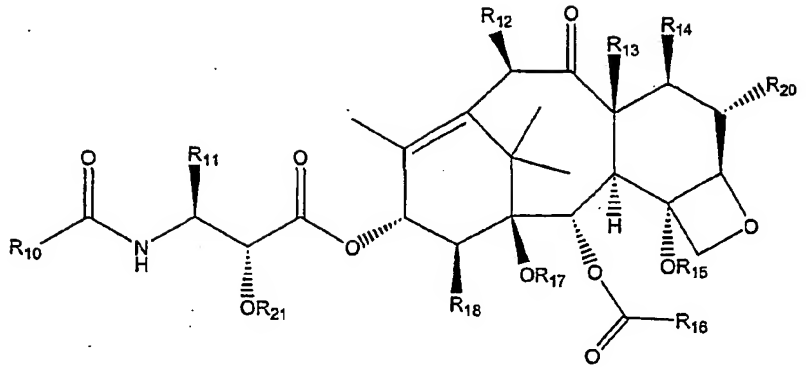


VI

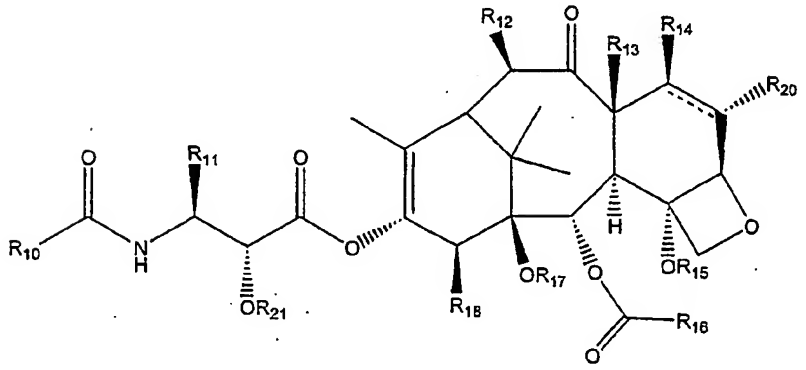
Double bonds have been omitted from the cyclohexane rings in the taxane skeleton represented by Structural Formula VI. It is to be understood that the basic taxane skeleton can include zero or one double bond in one or both cyclohexane rings, as indicated in the Taxol™ analogs and Structural Formulas VII and VIII below. A number of atoms have also been omitted from Structural Formula VI to indicate sites in which structural variation commonly occurs among Taxol™ analogs.

A wide variety of substituents can decorate the taxane skeleton without adversely affecting biological activity. Also, zero, one or both of the cyclohexane rings of a Taxol™ analog can have a double bond at the indicated positions. For example, substitution on the taxane skeleton with simply an oxygen atom indicates that hydroxyl, acyl, alkoxy or other oxygen-bearing substituent is commonly found at the site. It is to be understood that these and other substitutions on the taxane skeleton can be made without losing the ability to enhance and stabilize microtubule formation. Thus, the term "Taxol™ analog" is defined herein to mean a compound which has the basic Taxol™ skeleton and which stabilizes microtubule formation. The term taxane is defined herein to include compounds such as Taxol™ and the "Taxol™ analogs" described herein, or a pharmaceutically acceptable salt or solvate thereof.

Typically, the taxanes employed in the disclosed invention are represented by Structural Formula VII or VIII:



VII



VIII

R_{10} is an optionally substituted lower alkyl group, an optionally substituted phenyl group, $-SR_{19}$, $-NHR_{19}$ or $-OR_{19}$.

R_{11} is an optionally substituted lower alkyl group, an optionally substituted aryl group .

R_{12} is -H, -OH, lower alkyl, substituted lower alkyl, lower alkoxy, substituted lower alkoxy, -O-C(O)-(lower alkyl), -O-C(O)-(substituted lower alkyl), $-O-CH_2-O-$(lower alkyl) $-S-CH_2-O-$(lower alkyl).

R_{13} is -H, $-CH_3$, or, taken together with R_{14}, $-CH_2-$.

R_{14} is -H, -OH, lower alkoxy, -O-C(O)-(lower alkyl), substituted lower alkoxy, -O-C(O)-(substituted lower alkyl), $-O-CH_2-O-P(O)(OH)_2$, $-O-CH_2-O-$(lower alkyl), $-O-CH_2-S-$(lower alkyl) or, taken together with R_{20}, a double bond.

R_{15} -H, lower acyl, lower alkyl, substituted lower alkyl, alkoxymethyl, alkthiomethyl, -OC(O)-O(lower alkyl), -OC(O)-O(substituted lower alkyl), -OC(O)-NH(lower alkyl) or -OC(O)-NH(substituted lower alkyl).

R_{16} is phenyl or substituted phenyl.

R_{17} is -H, lower acyl, substituted lower acyl, lower alkyl, substituted, lower alkyl, (lower alkoxy)methyl or (lower alkyl)thiomethyl.

R_{18} -H, $-CH_3$ or, taken together with R_{17} and the carbon atoms to which R_{17} and R_{18} are bonded, a five or six membered a non-aromatic heterocyclic ring.

R_{19} is an optionally substituted lower alkyl group, an optionally substituted phenyl group.

R_{20} is -H or a halogen.

R_{21} is -H, lower alkyl, substituted lower alkyl, lower acyl or substituted lower acyl.

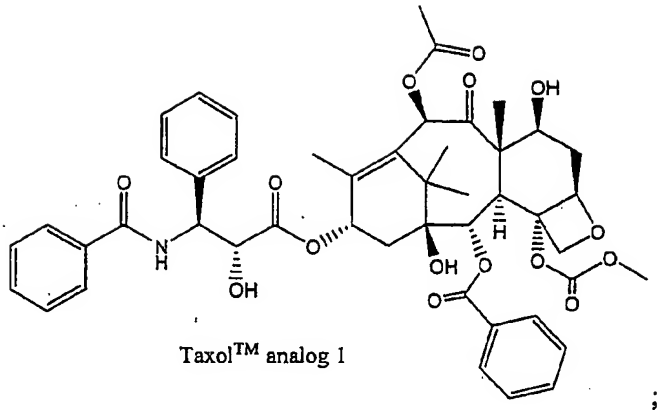
Preferably, the variables in Structural Formulas **VII** and **VIII** are defined as follows: R_{10} is phenyl, *tert*-butoxy, $-S-CH_2-CH-(CH_3)_2$, $-S-CH(CH_3)_3$, $-S-(CH_2)_3CH_3$, $-O-CH(CH_3)_3$, $-NH-CH(CH_3)_3$, $-CH=C(CH_3)_2$ or *para*-chlorophenyl; R_{11} is phenyl, $(CH_3)_2CHCH_2$-, -2-furanyl, cyclopropyl or *para*-toluyl; R_{12} is -H, -OH, CH_3CO- or $-(CH_2)_2$-*N*-morpholino; R_{13} is methyl, or, R_{13} and R_{14}, taken together, are $-CH_2$-;

R_{14} is -H, $-CH_2SCH_3$ or $-CH_2-O-P(O)(OH)_2$; R_{15} is CH_3CO-;

R_{16} is phenyl; R_{17} -H, or, R_{17} and R_{18}, taken together, are -O-CO-O-;

R_{18} is -H; R_{20} is -H or -F; and R_{21} is -H, $-C(O)-CHBr-(CH_2)_{13}-CH_3$ or $-C(O)-(CH_2)_{14}-CH_3$; $-C(O)-CH_2-CH(OH)-COOH$, $-C(O)-CH_2-O-C(O)-CH_2CH(NH_2)-CONH_2$, $-C(O)-CH_2-O--CH_2CH_2OCH_3$ or $-C(O)-O-C(O)-CH_2CH_3$.

Specific examples of Taxol™ analogs include the following compounds:



Taxol™ analog 1

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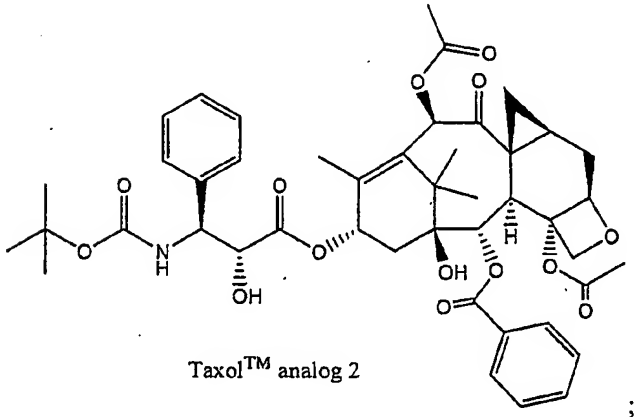

Taxol™ analog 2

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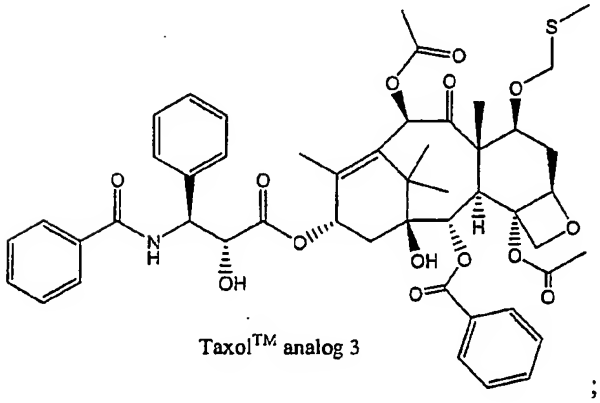

Taxol™ analog 3

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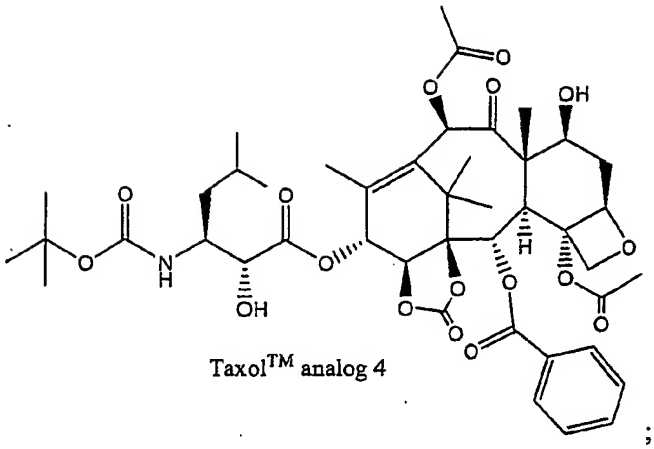
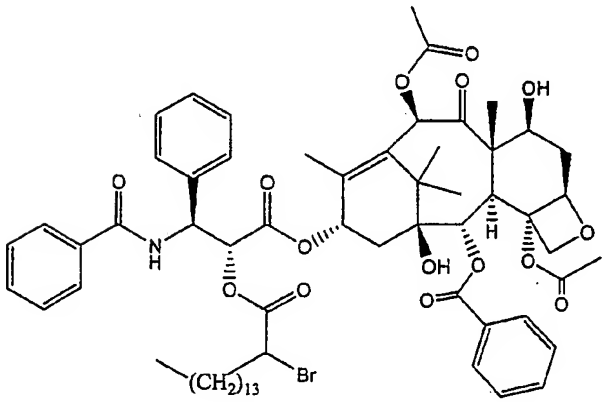
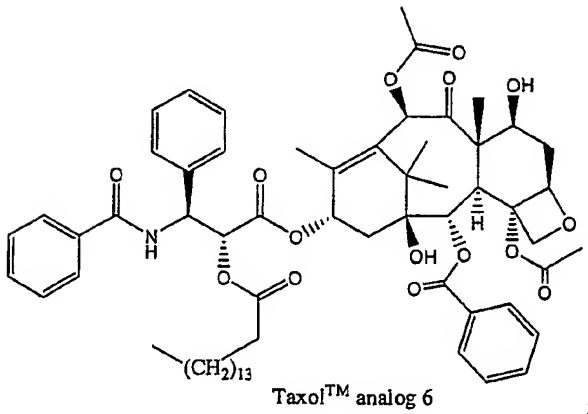


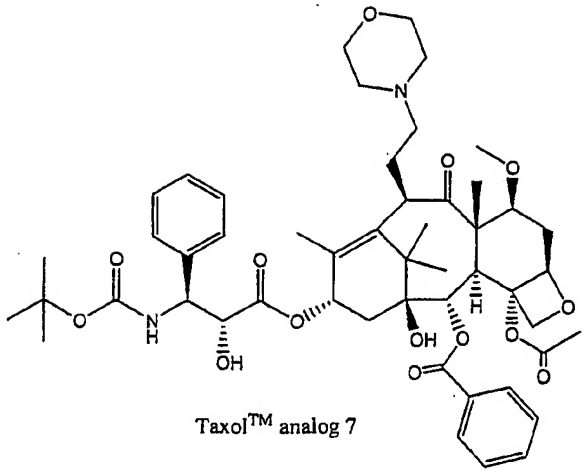
Taxol™ analog 4 ;



Taxol™ analog 5 ;



Taxol™ analog 6 ;



Taxol™ analog 7

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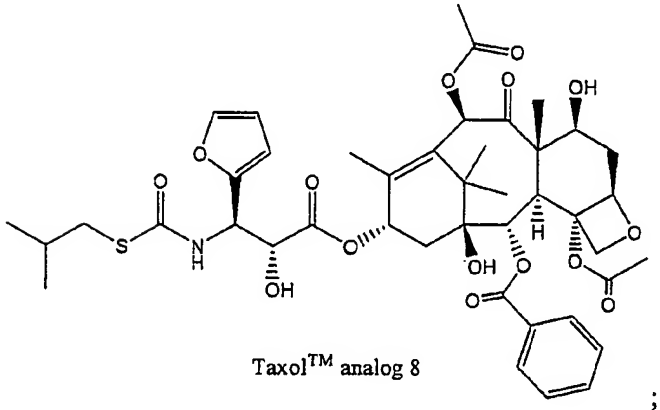

Taxol™ analog 8

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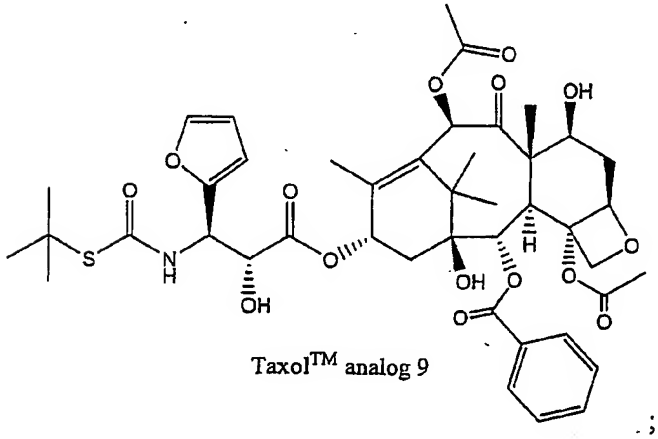

Taxol™ analog 9

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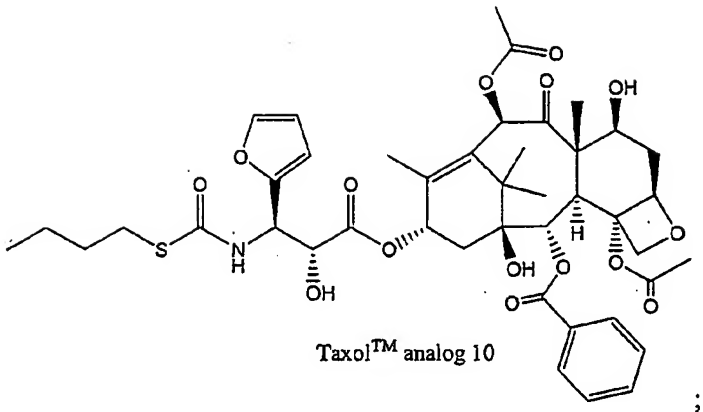
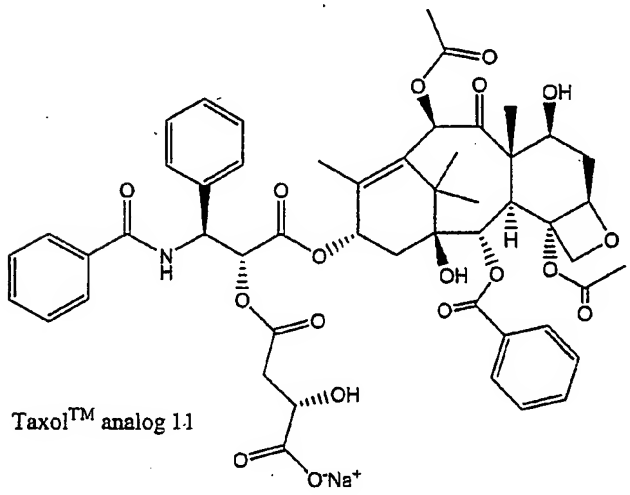
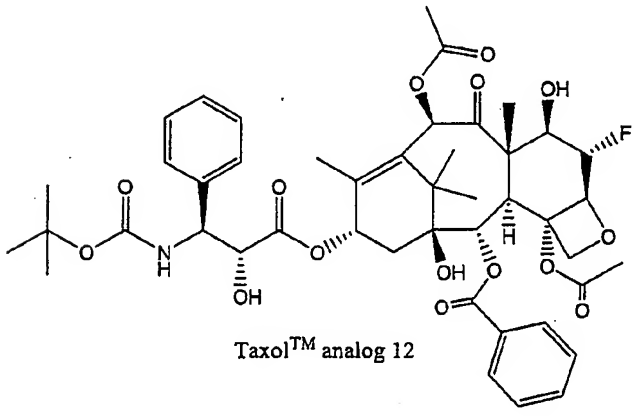


Taxol™ analog 10 ;



Taxol™ analog 11 ;



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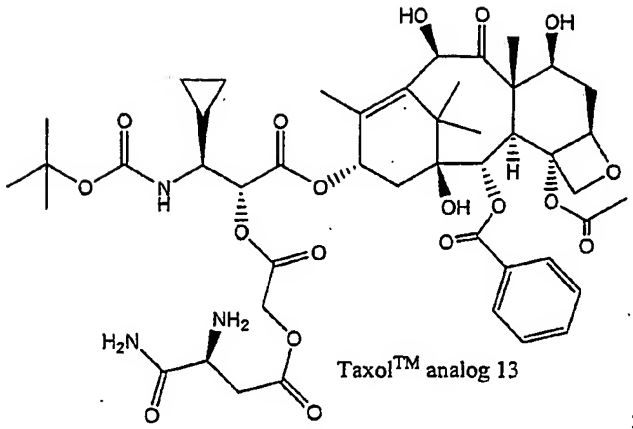
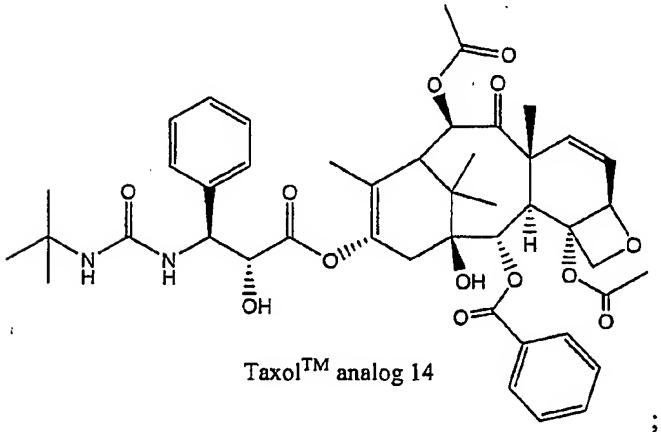
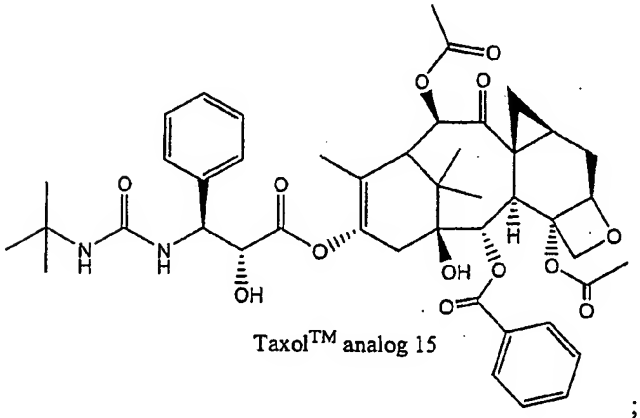


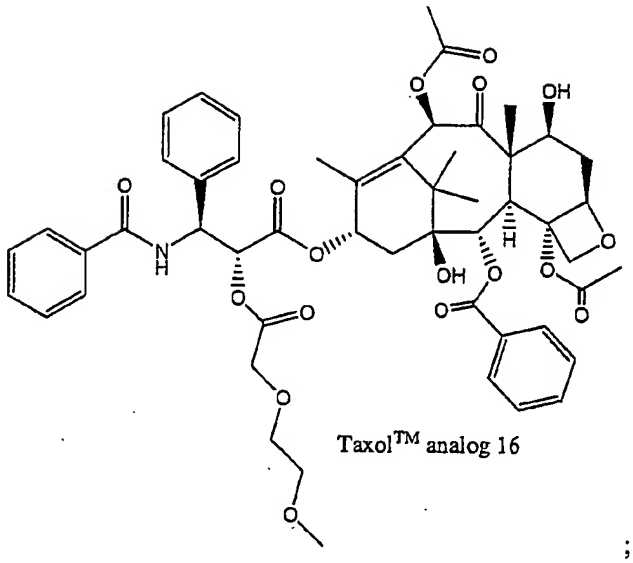
Taxol™ analog 13 ;



Taxol™ analog 14 ;



Taxol™ analog 15 ;



Taxol™ analog 16

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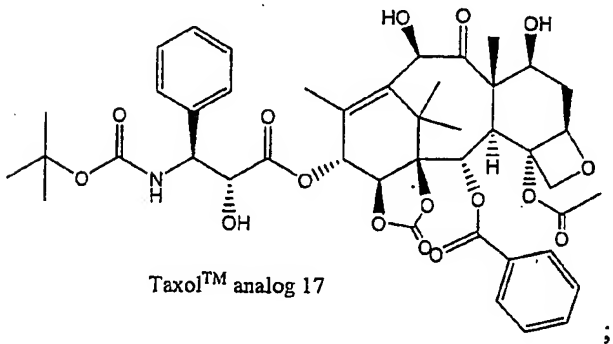

Taxol™ analog 17

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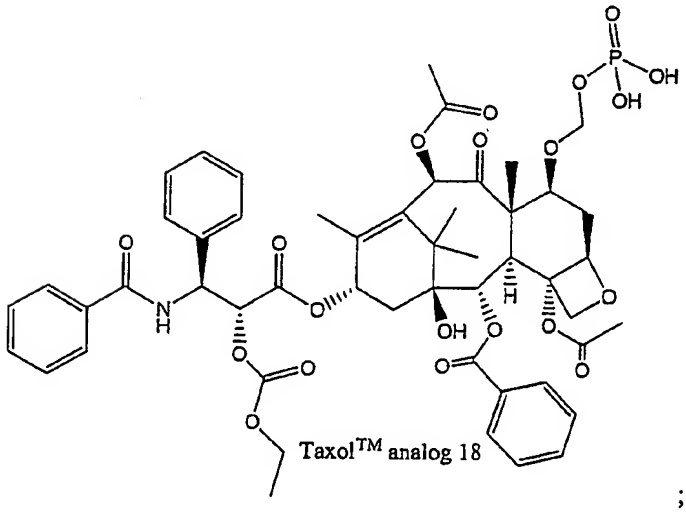

Taxol™ analog 18

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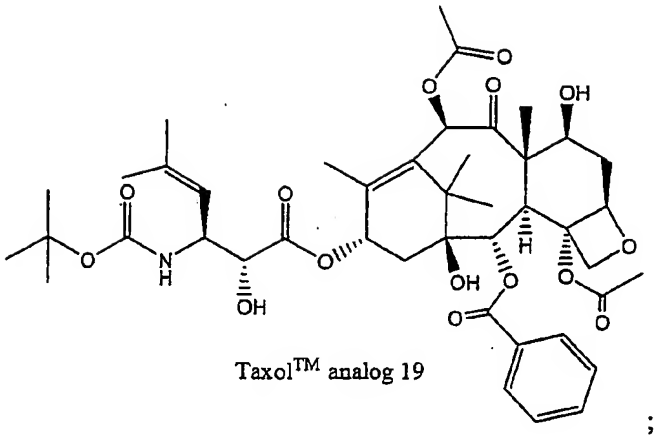

Taxol™ analog 19

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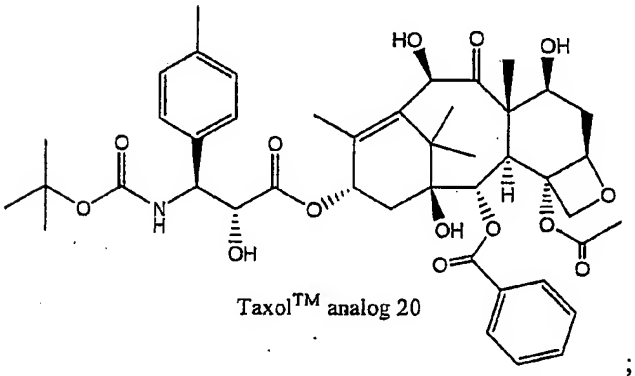

Taxol™ analog 20

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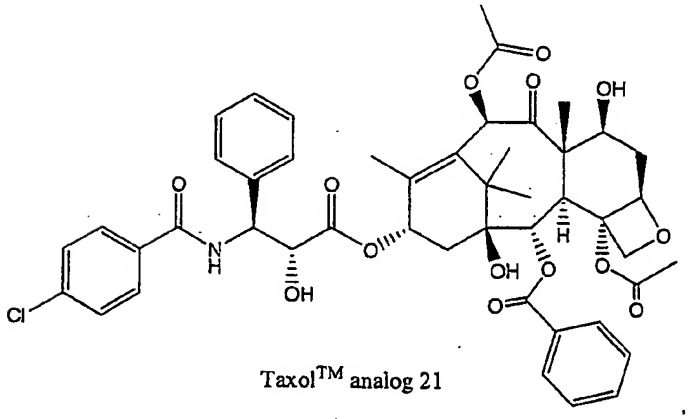
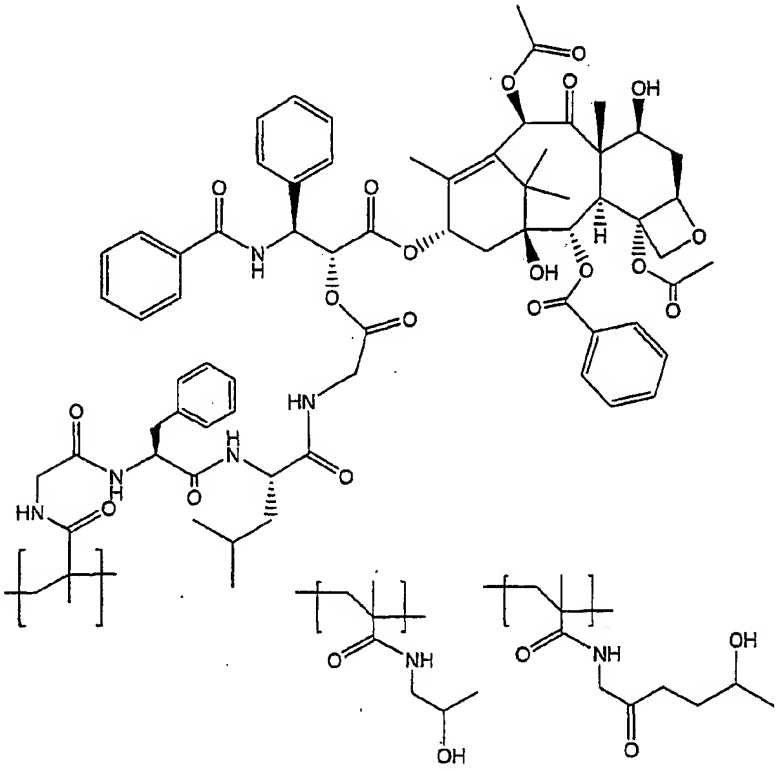


Taxol™ analog 21

A Taxol™ analog can also be bonded to or be pendent from a pharmaceutically acceptable polymer, such as a polyacrylamide. One example of a polymer of this type is Taxol™ analog 22, below, which has the structure of a polymer comprising a taxol analog group pendent from the polymer backbone. The

polymer is a terpolymer of the three monomer units shown. The term "Taxol™ analog", as it is used herein, includes such polymers.



Taxol™ analog 22

The compounds disclosed herein are believed to be particularly effective when co-administered with anti-cancer agents which act by arresting cells in the G2-M phases due to stabilized microtubules. Thus, the disclosed method preferably includes co-administered anti-cancer drugs which act by this mechanism. Examples of anti-cancer agents other than taxanes which act by arresting cells in the G2-M phases due to stabilized microtubules include without limitation the following marketed drugs and drugs in development: Erbulozole (also known as R-55104), Dolastatin 10 (also known as DLS-10 and NSC-376128), Mivobulin isethionate (also known as CI-980), Vincristine, NSC-639829, Discodermolide (also known as NVP-XX-A-296), ABT-751 (Abbott, also known as E-7010), Altorhyrtins (such as Altorhyrtin A and Altorhyrtin C), Spongistatins (such as Spongistatin 1,

Spongistatin 2, Spongistatin 3, Spongistatin 4, Spongistatin 5, Spongistatin 6, Spongistatin 7, Spongistatin 8, and Spongistatin 9), Cemadotin hydrochloride (also known as LU-103793 and NSC-D-669356), Epothilones (such as Epothilone A, Epothilone B, Epothilone C (also known as desoxyepothilone A or dEpoA), Epothilone D (also referred to as KOS-862, dEpoB, and desoxyepothilone B), Epothilone E, Epothilone F, Epothilone B N-oxide, Epothilone A N-oxide, 16-aza-epothilone B, 21-aminoepothilone B (also known as BMS-310705), 21-hydroxyepothilone D (also known as Desoxyepothilone F and dEpoF), 26-fluoroepothilone), Auristatin PE (also known as NSC-654663), Soblidotin (also known as TZT-1027), LS-4559-P (Pharmacia, also known as LS-4577), LS-4578 (Pharmacia, also known as LS-477-P), LS-4477 (Pharmacia), LS-4559 (Pharmacia), RPR-112378 (Aventis), Vincristine sulfate, DZ-3358 (Daiichi), FR-182877 (Fujisawa, also known as WS-9885B), GS-164 (Takeda), GS-198 (Takeda), KAR-2 (Hungarian Academy of Sciences), BSF-223651 (BASF, also known as ILX-651 and LU-223651), SAH-49960 (Lilly/Novartis), SDZ-268970 (Lilly/Novartis), AM-97 (Armad/Kyowa Hakko), AM-132 (Armad), AM-138 (Armad/Kyowa Hakko), IDN-5005 (Indena), Cryptophycin 52 (also known as LY-355703), AC-7739 (Ajinomoto, also known as AVE-8063A and CS-39.HCl), AC-7700 (Ajinomoto, also known as AVE-8062, AVE-8062A, CS-39-L-Ser.HCl, and RPR-258062A), Vitilevuamide, Tubulysin A, Canadensol, Centaureidin (also known as NSC-106969), T-138067 (Tularik, also known as T-67, TL-138067 and TI-138067), COBRA-1 (Parker Hughes Institute, also known as DDE-261 and WHI-261), H10 (Kansas State University), H16 (Kansas State University), Oncocidin A1 (also known as BTO-956 and DIME), DDE-313 (Parker Hughes Institute), Fijianolide B, Laulimalide, SPA-2 (Parker Hughes Institute), SPA-1 (Parker Hughes Institute, also known as SPIKET-P), 3-IAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-569), Narcosine (also known as NSC-5366), Nascapine, D-24851 (Asta Medica), A-105972 (Abbott), Hemiasterlin, 3-BAABU (Cytoskeleton/Mt. Sinai School of Medicine, also known as MF-191), TMPN (Arizona State University), Vanadocene acetylacetonate, T-138026 (Tularik), Monsatrol, Inanocine (also known as NSC-698666), 3-IAABE (Cytoskeleton/Mt. Sinai School of

Medicine), A-204197 (Abbott), T-607 (Tularik, also known as T-900607), RPR-115781 (Aventis), Eleutherobins (such as Desmethyleleutherobin, Desaetyleleutherobin, Isoeleutherobin A, and Z-Eleutherobin), Caribaeoside, Caribaeolin, Halichondrin B, D-64131 (Asta Medica), D-68144 (Asta Medica), Diazonamide A, A-293620 (Abbott), NPI-2350 (Nereus), Taccalonolide A, TUB-245 (Aventis), A-259754 (Abbott), Diozostatin, (-)-Phenylahistin (also known as NSCL-96F037), D-68838 (Asta Medica), D-68836 (Asta Medica), Myoseverin B, D-43411 (Zentaris, also known as D-81862), A-289099 (Abbott), A-318315 (Abbott), HTI-286 (also known as SPA-110, trifluoroacetate salt) (Wyeth), D-82317 (Zentaris), D-82318 (Zentaris), SC-12983 (NCI), Resverastatin phosphate sodium, BPR-0Y-007 (National Health Research Institutes), and SSR-250411 (Sanofi).

A "straight chained hydrocarbyl group" is an alkylene group, *i.e.*, $-(CH_2)_y-$, with one, or more (preferably one) internal methylene groups optionally replaced with a linkage group. y is a positive integer (*e.g.*, between 1 and 10), preferably between 1 and 6 and more preferably 1 or 2. A "linkage group" refers to a functional group which replaces a methylene in a straight chained hydrocarbyl. Examples of suitable linkage groups include a ketone (-C(O)-), alkene, alkyne, phenylene, ether (-O-), thioether (-S-), or amine ($-N(R^a)-$), wherein R^a is defined below. A preferred linkage group is $-C(R_5R_6)-$, wherein R_5 and R_6 are defined above. Suitable substituents for an alkylene group and a hydrocarbyl group are those which do not substantially interfere with the anti-cancer activity of the bis(thiohydrazide) amides and taxanes. R_5 and R_6 are preferred substituents for an alkylene or hydrocarbyl group represented by Y.

An aliphatic group is a straight chained, branched or cyclic non-aromatic hydrocarbon which is completely saturated or which contains one or more units of unsaturation. Typically, a straight chained or branched aliphatic group has from 1 to about 20 carbon atoms, preferably from 1 to about 10, and a cyclic aliphatic group has from 3 to about 10 carbon atoms, preferably from 3 to about 8. An aliphatic group is preferably a straight chained or branched alkyl group, *e.g.*, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, pentyl or octyl, or a cycloalkyl group with 3 to about 8 carbon atoms. A C1-C20 straight chained or

branched alkyl group or a C3-C8 cyclic alkyl group is also referred to as a "lower alkyl" group.

The term "aromatic group" may be used interchangeably with "aryl," "aryl ring," "aromatic ring," "aryl group" and "aromatic group." Aromatic groups include carbocyclic aromatic groups such as phenyl, naphthyl, and anthracyl, and heteroaryl groups such as imidazolyl, thienyl, furanyl, pyridyl, pyrimidyl, pyranyl, pyrazolyl, pyrroyl, pyrazinyl, thiazole, oxazolyl, and tetrazole. The term "heteroaryl group" may be used interchangeably with "heteroaryl," "heteroaryl ring," "heteroaromatic ring" and "heteroaromatic group." The term "heteroaryl," as used herein, means a mono-or multi-cyclic aromatic heterocycle which comprise at least one heteroatom such as nitrogen, sulfur and oxygen, but may include 1, 2, 3 or 4 heteroatoms per ring. Aromatic groups also include fused polycyclic aromatic ring systems in which a carbocyclic aromatic ring or heteroaryl ring is fused to one or more other heteroaryl rings. Examples include benzothienyl, benzofuranyl, indolyl, quinolinyl, benzothiazole, benzooxazole, benzimidazole, quinolinyl, isoquinolinyl and isoindolyl.

The term "arylene" refers to an aryl group which is connected to the remainder of the molecule by two other bonds. By way of example, the structure of a 1,4-phenylene group is shown below:

Substituents for an arylene group are as described below for an aryl group.

Non-aromatic heterocyclic rings are non-aromatic rings which include one or more heteroatoms such as nitrogen, oxygen or sulfur in the ring. The ring can be five, six, seven or eight-membered. Examples include tetrahydrofuranyl, tetrahydrothiophenyl, morpholino, thiomorpholino, pyrrolidinyl, piperazinyl, piperidinyl, and thiazolidinyl.

Suitable substituents on an aliphatic group (including an alkylene group), non-aromatic heterocyclic group, benzylic or aryl group (carbocyclic and heteroaryl) are those which do not substantially interfere with the anti-cancer activity of the bis(thiohydrazide) amides and taxanes.. A substituent substantially interferes with

anti-cancer activity when the anti-cancer activity is reduced by more than about 50% in a compound with the substituent compared with a compound without the substituent. Examples of suitable substituents include $-R^a$, -OH, -Br, -Cl, -I, -F, $-OR^a$, $-O-COR^a$, $-COR^a$, -CN, $-NO_2$, -COOH, $-SO_3H$, $-NH_2$, $-NHR^a$, $-N(R^aR^b)$, $-COOR^a$, -CHO, $-CONH_2$, $-CONHR^a$, $-CON(R^aR^b)$, $-NHCOR^a$, $-NR^cCOR^a$, $-NHCONH_2$, $-NHCONR^aH$, $-NHCON(R^aR^b)$, $-NR^cCONH_2$, $-NR^cCONR^aH$, $-NR^cCON(R^aR^b)$, $-C(=NH)-NH_2$, $-C(=NH)-NHR^a$, $-C(=NH)-N(R^aR^b)$, $-C(=NR^c)-NH_2$, $-C(=NR^c)-NHR^a$, $-C(=NR^c)-N(R^aR^b)$, $-NH-C(=NH)-NH_2$, $-NH-C(=NH)-NHR^a$, $-NH-C(=NH)-N(R^aR^b)$, $-NH-C(=NR^c)-NH_2$, $-NH-C(=NR^c)-NHR^a$, $-NH-C(=NR^c)-N(R^aR^b)$, $-NR^dH-C(=NH)-NH_2$, $-NR^d-C(=NH)-NHR^a$, $-NR^d-C(=NH)-N(R^aR^b)$, $-NR^d-C(=NR^c)-NH_2$, $-NR^d-C(=NR^c)-NHR^a$, $-NR^d-C(=NR^c)-N(R^aR^b)$, $-NHNH_2$, $-NHNHR^a$, $-NHR^aR^b$, $-SO_2NH_2$, $-SO_2NHR^a$, $-SO_2NR^aR^b$, $-CH=CHR^a$, $-CH=CR^aR^b$, $-CR^c=CR^aR^b$, $-CR^c=CHR^a$, $-CR^c=CR^aR^b$, $-CCR^a$, -SH, $-SR^a$, $-S(O)R^a$, $-S(O)_2R^a$.

R^a-R^d are each independently an alkyl group, aromatic group, non-aromatic heterocyclic group or $-N(R^aR^b)$, taken together, form an optionally substituted non-aromatic heterocyclic group. The alkyl, aromatic and non-aromatic heterocyclic group represented by R^a-R^d and the non-aromatic heterocyclic group represented by $-N(R^aR^b)$ are each optionally and independently substituted with one or more groups represented by $R^{\#}$.

$R^{\#}$ is R^+, $-OR^+$, -O(haloalkyl), $-SR^+$, $-NO_2$, -CN, -NCS, $-N(R^+)_2$, $-NHCO_2R^+$, $-NHC(O)R^+$, $-NHNHC(O)R^+$, $-NHC(O)N(R^+)_2$, $-NHNHC(O)N(R^+)_2$, $-NHNHCO_2R^+$, $-C(O)C(O)R^+$, $-C(O)CH_2C(O)R^+$, $-CO_2R^+$, $-C(O)R^+$, $-C(O)N(R^+)_2$, $-OC(O)R^+$, $-OC(O)N(R^+)_2$, $-S(O)_2R^+$, $-SO_2N(R^+)_2$, $-S(O)R^+$, $-NHSO_2N(R^+)_2$, $-NHSO_2R^+$, $-C(=S)N(R^+)_2$, or $-C(=NH)-N(R^+)_2$.

R^+ is –H, a C1-C4 alkyl group, a monocyclic heteroaryl group, a non-aromatic heterocyclic group or a phenyl group optionally substituted with alkyl, haloalkyl, alkoxy, haloalkoxy, halo, -CN, $-NO_2$, amine, alkylamine or dialkylamine. Optionally, the group $-N(R^+)_2$ is a non-aromatic heterocyclic group, provided that non-aromatic heterocyclic groups represented by R^+ and $-N(R^+)_2$ that comprise a secondary ring amine are optionally acylated or alkylated.

Preferred substituents for a phenyl group, including phenyl groups represented by R_1-R_4, include C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, phenyl, benzyl, pyridyl, -OH, $-NH_2$, -F, -Cl, -Br, -I, $-NO_2$ or -CN.

Preferred substituents for an aliphatic group, including aliphatic groups represented by R_1-R_4, include C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, phenyl, benzyl, pyridyl, -OH, $-NH_2$, -F, -Cl, -Br, -I, $-NO_2$ or -CN.

Preferred substituents for a cycloalkyl group, including cycloalkyl groups represented by R_1 and R_2, are alkyl groups, such as a methyl or ethyl groups.

Also included in the present invention are pharmaceutically acceptable salts of the bis(thiohydrazide) amides and taxanes employed herein. These compounds can have one or more sufficiently acidic protons that can react with a suitable organic or inorganic base to form a base addition salt. Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like, and organic bases such as alkoxides, alkyl amides, alkyl and aryl amines, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide, potassium carbonate, and the like.

For example, pharmaceutically acceptable salts of bis(thiohydrazide) amides and taxanes employed herein (*e.g.*, those represented by Structural Formulas **I-VI**, Compounds **1-18**, and Taxol™ analogs **1-22**) are those formed by the reaction of the compound with one equivalent of a suitable base to form a monovalent salt (*i.e.*, the compound has single negative charge that is balanced by a pharmaceutically acceptable counter cation, *e.g.*, a monovalent cation) or with two equivalents of a suitable base to form a divalent salt (*e.g.*, the compound has a two-electron negative charge that is balanced by two pharmaceutically acceptable counter cations, *e.g.*, two pharmaceutically acceptable monovalent cations or a single pharmaceutically acceptable divalent cation). Divalent salts of the bis(thiohydrazide amides) are preferred. "Pharmaceutically acceptable" means that the cation is suitable for administration to a subject. Examples include Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+} and NR_4^+, wherein each R is independently hydrogen, an optionally substituted aliphatic group (*e.g.*, a hydroxyalkyl group, aminoalkyl group or ammoniumalkyl group) or

optionally substituted aryl group, or two R groups, taken together, form an optionally substituted non-aromatic heterocyclic ring optionally fused to an aromatic ring. Generally, the pharmaceutically acceptable cation is Li^+, Na^+, K^+, $NH_3(C_2H_5OH)^+$ or $N(CH_3)_3(C_2H_5OH)^+$, and more typically, the salt is a disodium or dipotassium salt, preferably the disodium salt.

Bis(thiohydrazide) amides and taxanes employed herein having a sufficiently basic group, such as an amine can react with an organic or inorganic acid to form an acid addition salt. Acids commonly employed to form acid addition salts from compounds with basic groups are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as p-toluenesulfonic acid, methanesulfonic acid, oxalic acid, p-bromophenyl-sulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such salts include the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, gamma-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, and the like.

Particular salts of the bis(thiohydrazide amide) compounds described herein can be prepared according to methods described in copending, co-owned Patent Application Serial No. 60/582,596, filed June 23, 2004.

The neutral bis(thiohydrazide) amides can be prepared according to methods described in U.S. Patent Nos. 6,800,660, and 6,762,204, both entitled "Synthesis of Taxol Enhancers" and also according to methods described in the co-pending and co-owned U.S. Pat. Appl. Ser. Nos. 10/345,885 filed January 15, 2003, and

10/758,589, January 15, 2004. The entire teachings of each document referred to in this application is expressly incorporated herein by reference.

It will also be understood that certain compounds employed in the invention may be obtained as different stereoisomers (*e.g.*, diastereomers and enantiomers) and that the invention includes all isomeric forms and racemic mixtures of the disclosed compounds and methods of treating a subject with both pure isomers and mixtures thereof, including racemic mixtures. Stereoisomers can be separated and isolated using any suitable method, such as chromatography.

As used herein, a "subject" is a mammal, preferably a human, but can also be an animal in need of veterinary treatment, *e.g.*, companion animals (*e.g.*, dogs, cats, and the like), farm animals (*e.g.*, cows, sheep, pigs, horses, and the like) and laboratory animals (*e.g.*, rats, mice, guinea pigs, and the like).

The bis(thiohydrazide) amides and taxanes employed herein can be administered to a subject by any conventional method of drug administration for treatment of cancerous disorders, for example, orally in capsules, suspensions or tablets or by parenteral administration. Parenteral administration can include, for example, systemic administration, such as by intramuscular, intravenous, subcutaneous, or intraperitoneal injection. In specific embodiments, oral, parenteral, or local administration are preferred modes of administration for treatment of cancer. Preferably, the mode of administration is intravenous.

An effective amount of a bis(thio-hydrazide) amide, a taxane, or a platinum anticancer compound is a quantity in which anti-cancer effects are normally achieved. With respect to a particular compound in the method (e.g., the bis(thio-hydrazide) amide, the taxane, or the platinum anticancer compound), an "effective amount" is the quantity in which a greater anti-cancer effect is achieved when the particular compound is co-administered with the other compounds in the method compared with when the particular compound is administered alone. The compounds of the method can be co-administered to the subject as part of the same pharmaceutical composition or, alternatively, as separate pharmaceutical compositions. When administered as separate pharmaceutical compositions, the

compounds of the method can be administered simultaneously or at different times, provided that the enhancing effect of the compounds in combination is retained.

As used herein, "treating a subject with a cancer," or similar terms, includes achieving, partially or substantially, one or more of the following: arresting the growth or spread of a cancer, reducing the extent of a cancer (*e.g.*, reducing size of a tumor or reducing the number of affected sites), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components).

In various embodiments, cancer can include human sarcomas and carcinomas, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrobm's macroglobulinemia, and heavy chain disease.

In some embodiments, cancer can include leukemias e.g.,acute and/or chronic leukemias, e.g., lymphocytic leukemia (e.g., as exemplified by the p388 (murine) cell line), large granular lymphocytic leukemia, and lymphoblastic

leukemia; T-cell leukemias, e.g., T-cell leukemia (e.g., as exemplified by the CEM, Jurkat, and HSB-2 (acute), YAC-1(murine) cell lines), T-lymphocytic leukemia, and T-lymphoblastic leukemia; B cell leukemia (e.g., as exemplified by the SB (acute) cell line), and B-lymphocytic leukemia; mixed cell leukemias, e.g., B and T cell leukemia and B and T lymphocytic leukemia; myeloid leukemias, e.g., granulocytic leukemia, myelocytic leukemia (e.g., as exemplified by the HL-60 (promyelocyte) cell line), and myelogenous leukemia (e.g., as exemplified by the K562(chronic)cell line); neutrophilic leukemia; eosinophilic leukemia; monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); myelomonocytic leukemia; Naegeli-type myeloid leukemia; and nonlymphocytic leukemia. Other examples of leukemias are described in Chapter 60 of *The Chemotherapy Sourcebook*, Michael C. Perry Ed., Williams & Williams (1992) and Section 36 of *Holland Frie Cancer Medicine* 5th Ed., Bast et al. Eds., B.C. Decker Inc. (2000). The entire teachings of the preceding references are incorporated herein by reference.

In certain embodiments, cancer can include non-solid tumors such as multiple myeloma, T-leukemia (e.g., as exemplified by Jurkat and CEM cell lines); B-leukemia (e.g., as exemplified by the SB cell line); promyelocytes (e.g., as exemplified by the HL-60 cell line); uterine sarcoma (e.g., as exemplified by the MES-SA cell line); monocytic leukemia (e.g., as exemplified by the THP-1(acute) cell line); and lymphoma (e.g., as exemplified by the U937 cell line).

In some embodiments, cancer can include colon cancer, pancreatic cancer, melanoma, renal cancer, sarcoma, breast cancer, ovarian cancer, lung cancer. stomach cancer, bladder cancer and cervical cancer.

In some embodiments, the disclosed methods can be particularly effective at treating subjects whose cancer has become "multi-drug resistant". A cancer which initially responded to an anti-cancer drug becomes resistant to the anti-cancer drug when the anti-cancer drug is no longer effective in treating the subject with the cancer. For example, many tumors can initially respond to treatment with an anti-cancer drug by decreasing in size or even going into remission, only to develop resistance to the drug. Drug resistant tumors are characterized by a resumption of their growth and/or reappearance after having seemingly gone into remission,

despite the administration of increased dosages of the anti-cancer drug. Cancers that have developed resistance to two or more anti-cancer drugs are said to be "multi-drug resistant". For example, it is common for cancers to become resistant to three or more anti-cancer agents, often five or more anti-cancer agents and at times ten or more anti-cancer agents.

The bis(thiohydrazide) amides and taxanes employed herein can be administered to the subject in conjunction with an acceptable pharmaceutical carrier or diluent as part of a pharmaceutical composition for treatment cancer therapy. Formulation of the compound to be administered will vary according to the route of administration selected (*e.g.*, solution, emulsion, capsule, and the like). Suitable pharmaceutically acceptable carriers may contain inert ingredients which do not unduly inhibit the biological activity of the compounds. The pharmaceutically acceptable carriers should be biocompatible, *i.e.*, non-toxic, non-inflammatory, non-immunogenic and devoid of other undesired reactions upon the administration to a subject. Standard pharmaceutical formulation techniques can be employed, such as those described in Remington's Pharmaceutical Sciences, *ibid.* Suitable pharmaceutical carriers for parenteral administration include, for example, sterile water, physiological saline, bacteriostatic saline (saline containing about 0.9% mg/ml benzyl alcohol), phosphate-buffered saline, Hank's solution, Ringer's-lactate and the like. Methods for encapsulating compositions (such as in a coating of hard gelatin or cyclodextran) are known in the art (Baker, *et al.*, "Controlled Release of Biological Active Agents", John Wiley and Sons, 1986).

In certain embodiments, one or more compounds of the invention and one or more other the therapies (*e.g.*, prophylactic or therapeutic agents) are cyclically administered. Cycling therapy involves the administration of a first therapy (*e.g.*, a first prophylactic or therapeutic agents) for a period of time, followed by the administration of a second therapy (*e.g.*, a second prophylactic or therapeutic agents) for a period of time, followed by the administration of a third therapy (*e.g.*, a third prophylactic or therapeutic agents) for a period of time and so forth, and repeating this sequential administration, *i.e.*, the cycle in order to reduce the development of

resistance to one of the agents, to avoid or reduce the side effects of one of the agents, and/or to improve the efficacy of the treatment.

In various embodiments, the methods herein can include administration prior to or concurrenty with the bis(thiohydrazide) amide/taxane combination, agents that can reduce acute irritation or allergic reaction to administration, e.g., an anti-inflammatory such as Decadron® (dexamethasone, e.g., 10 mg intravenously), an antihistamine such as Benadryl® (diphenhydramine, e.g., 50 mg intravenously), an antacid such as Zantac® (ranitidine hydrochloride, e.g., 50 mg intravenously), and the like.

EXEMPLIFICATION

Example 1: Measurement of Heat Shock Protein 70 (Hsp70)

Plasma Hsp70 was measured by a sandwich ELISA kit (Stressgen Bioreagents Victoria, British Columbia, CANADA) according to a modified protocol in house. In brief, Hsp70 in plasma specimens and serial concentrations of Hsp70 standard were captured onto 96-well plate on which anti-Hsp70 antibody was coated. Then captured Hsp70 was detected with a biotinylated anti-Hsp70 antibody followed by incubation with europium-conjugated streptavidin. After each incubation unbound materials were removed by washing. Finally, antibody-Hsp70 complex was measured by time resolved fluorometry of europium. Concentration of Hsp70 was calculated from a standard curve.

Example 2: Measurement of Natural Killer Cell Cytotoxic Activity

The following procedure can be employed to assay NK cell activity in a subject. The procedure is adapted from Kantakamalakul W, Jaroenpool J, Pattanapanyasat K. A novel enhanced green fluorescent protein (EGFP)-K562 flow cytometric method for measuring natural killer (NK) cell cytotoxic activity. J Immunol Methods. 2003 Jan 15; 272:189-197, the entire teachings of which are incorporated herein by reference.

Materials and methods: Human erythroleukaemic cell line, K562, was obtained from American Type Culture Collection (CCL-243, American Type Culture Collection, Manassas, VA), and cultured in RPMI-1640 medium (Cat#11875-093Gibco Invitrogen Corp, Carlsbad, CA) supplemented with 10% heat inactivated fetal calf serum (Gibco), 2mM L-glutamin, 100 μg/ml streptomycin and 100 IU/ml penicillin at 37° C with 5% CO_2. K562 cells were transduced with retroviral vector which encode green fluorescent protein (eGFP). Stable cell line was selected with antibiotic, G418. About 99.6% G418 resistant cells were eGFP positive after section.

The subject's peripheral blood mononuclear cells (PBMCs) were prepared by clinical study sites and received in BD Vacutainer Cell Preparation Tube with sodium heparin (Product Number: 362753, Becton Dickinson, Franklin Lakes, NJ).

Two-fold serial dilution of 800 μl effector cells (patient's PBMC) starting at concentration of $1X10^6$ cells/mL were put into four individual polystyrene 12X75-mm tubes. Log phase growing target cells (K562/eGFP) were adjusted with growth medium (RPMI-1640) to a concentration of $1X10^5$ cells/mL and 100 μL targets then added into the tubes to provide effector/target (E/T) ratios of 80:1, 40:1, 20:1, 10:1. Effector cells alone and target cells alone were used as controls. All tubes were incubated at 37° C with 5% CO_2 for about 3.5 hr. Ten microliters of propidium iodide (PI) at a concentration of 1 mg/mL was added t each tube including effector and target control tubes and then incubated at room temperature for 15 min.

Cytotoxic activity was analyzed with a FACSCalibur flow cytometer (Becton Dickinson). Linear amplification of the forward and side scatter (FSC/SSC) signals, as well as logarithmic amplification of eGFP and PI emission in green and red fluorescence were obtained. Ten thousand events per sample tube with no gating for acquisition were collected for analysis. Data analysis for two-parameter dot plots for eGFP versus PI was performed using CELLQuest (Becton Dickinson Biosciences) software to enumerate live and dead target cells. Debris and dead cells were excluded by setting a threshold of forward light scatter.

Example 3: The Disclosed Combination Therapy Induces Hsp70

A Phase I trial was conducted for combined administration of a bis(thio-hydrazide) amide (Compound (1)) and a taxane (paclitaxel) to human subjects with various advanced solid tumors. Compound (1) and paclitaxel were co-administered intravenously over 3 hours every 3 weeks. Starting doses were 44 milligrams/meter^2 (mg/m2, or 110 micromoles/meter^2 (μmol/m2)) Compound (1) and 135 mg/m2 (158 μmol/m2) paclitaxel . Paclitaxel was then increased to 175 mg/m2 (205 μmol/m2), followed by escalation of Compound (1) to establish the maximum tolerated dose based on first cycle toxicity in 3 to 6 patients at each dose level. Pharmacokinetic (PK) studies were performed during cycle 1 using liquid chromatography/mass spectrometry (LC/MS) to measure both compounds in plasma. Heat shock protein 70 (Hsp70) was measured in plasma before and after treatment. 35 patients were evaluated at 8 dose levels, including paclitaxel at 135

mg/m2 (158 μmol/m2) and Compound (1) at 44 mg/m2, and paclitaxel at 175 mg/m2 (205 μmol/m2) and Compound (1) at a doses ranging among 44-525 mg/m2 (110-1311 μmol /m2). Table 1 shows the eight different doses #1-#8 in mg/m^2 and μmol/m^2.

Table 1	#1	#2	#3	#4	#5	#6	#7	#8
Compound (1), mg/m^2	44	44	88	175	263	350	438	525
Compound (1), μmol/m^2	110	110	220	437	657	874	1094	1311
Paclitaxel, mg/m^2	135	175	175	175	175	175	175	175
Paclitaxel, μmol/m^2	158	205	205	205	205	205	205	205

No serious effects specifically attributable to Compound (1) were observed. Paclitaxel dose limiting toxicities occurred in a single patient in each of the top three dose levels (neutropenia, arthralgia, and febrile neutropenia with mucositis) resulting in cohort expansion. Compound (1) exhibited linear PK that was unaffected by paclitaxel dose, and was rapidly eliminated from plasma with terminal-phase half life of 0.94 ± 0.23 hours (h) and total body clearance of 28 ± 8 Liters/hour/meter^2 (L/h/m^2). Its apparent volume of distribution was comparable to total body water (V_{ss} 23 ± 16 L/m^2). Paclitaxel PK appeared to be moderately dependent on the Compound (1) dose, as indicated by a significant trend toward decreasing clearance, and increase in peak plasma concentration and V_{ss}, but without affecting the terminal phase half-life. These observations are consistent with competitive inhibition of paclitaxel hepatic metabolism. Increased toxicity at higher dose levels was consistent with a moderate increase in systemic exposure to paclitaxel. Induction of Hsp70 protein in plasma was dose dependent, peaking between about 8 hours to about 24 hours after dosing.

FIGs 1A, 1B, and 1C are bar graphs showing the percent increase in Hsp70 plasma levels associated with administration of the Compound (1)/paclitaxel combination therapy at 1 hour (FIG 1A), 5 hours (FIG 1B), and 8 hours (FIG 1C) after administration. Significant rises in Hsp70 levels occurred for at least one patient at the 88 mg/m2 (220 μmol /m2) Compound (1) dose, where Hsp70 levels nearly doubled in a percent increase of about 90%. At the 175 mg/m2 (437

μmol/m2) Compound (1) dose, Hsp70 concentrations more than doubled in two patients; at the 263 mg/m2 (657 μmol/m2) Compound (1) dose, Hsp70 concentrations roughly doubled in two patients and increased by more than 250% in a third patient; at the 350 mg/m2 (874 μmol/m2) Compound (1) dose, Hsp70 concentrations increased more than 200% in all patients and increased by as much as 500% in two patients; at the 438 mg/m2 (1094 μmol/m2) Compound (1) dose, Hsp70 concentrations roughly doubled in two patients, increased by over 2005 in one patient, and increased by as much as 500% in another patient.

Time to progression will be measured as the time from patient randomization to the time the patient is first recorded as having tumor progression according to the RECIST (Response Evaluation Criteria in Solid Tumors Group) criteria; see Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16, the entire teachings of which are incorporated by reference. Death from any cause will be considered as progressed.

Time to progression can be performed on the randomized sample as well as the efficacy sample. Treatment groups can be compared using the log-rank test and Kaplan-Meier curves of time to progression can be presented.

FIG 2 is a Kaplan-Meier graph of time-to-progression (resumption of cancer growth) in studies of various combinations of platinum anticancer drugs and taxanes. Also shown is the disclosed combination of a bisthiohydrazide (Compound (1)), a taxane (paclitaxel) and also a platinum anticancer drug, carboplatin. The preliminary data in show that the disclosed method is superior to the platin/taxane combination alone.

Thus, the combination of a bi(thio-hydrazide) amide and taxane dramatically increased plasma Hsp70 levels in patients, giving significant increases for patients at a combined paclitaxel dose of 175 mg/m2 (205 μmol/m2) and Compound (1) doses ranging from 88 through 438 mg/m2 (220-1094 μmol/m2). Moreover, the combination was well-tolerated, with adverse events consistent with those expected for paclitaxel alone.

Example 4: A Phase 1/2 Study Shows the Effects of the Disclosed Combination Therapy with Carboplatin for Treating Non-Small Cell Lung Carcinoma

The following study of Compound (1) and paclitaxel in patients with non-small cell lung carcinoma was initiated based on the biological activity shown by the results of the above Phase I study, where the combined administration Compound (1) and paclitaxel led to dose-related Hsp70 induction.

Phase 1 (safety/PK/MTD (maximum tolerated dose) was followed by a Phase 2 randomized two arm portion. Two dose levels were evaluated in Phase 1.

Cohort 1 was dosed with carboplatin AUC (area under the curve) 6, paclitaxel 175 mg/m2 and Compound (1) 233 mg/m2. If the maximum tolerated dose was not observed, Cohort 2 was enrolled with carboplatin AUC 6, paclitaxel 200 mg/m2 and Compound (1) 266 mg/m2.

Dosing was IV q 3 weeks for up to 6 cycles in the absence of dose-limiting toxicity or progression. In the phase 2 portion, 86 patients are planned to be randomized 1:1 to carboplatin AUC 6 + paclitaxel 200 mg/m2 IV q 3 weeks or carboplatin AUC 6, paclitaxel 200 mg/m2 and Compound (1) 266 mg/m2. The phase 2 primary endpoint is time to progression, with secondary endpoints of response rate, survival, and quality of life. Study pharmacodynamic parameters include NK cell activity and Hsp70 level.

Sixteen patients were treated in Phase 1, 7 in Cohort 1, and 9 in Cohort 2. No first cycle dose-limiting toxicities were seen in either cohort. Phase adverse effects (AEs) included (usually Grade 1-2) arthralgia and myalgia, peripheral neuropathy, rash, nausea, and vomiting, fatigue, alopecia, edema, dehydration, constipation, and decreased blood counts. Eleven patients completed 6 cycles of therapy. Eight patients (50%) achieved a partial response (PR). Seven of the 8 patients with evaluable samples showed increased NK cell activity when assayed 7 days after the second dose.

The carboplatin:paclitaxel:Compound (1) combination is well tolerated at the dose levels studied, and the overall safety profile appears similar to that of carboplatin:paclitaxel alone. Encouraging clinical activity was observed, as well as

correlative NK activity that supports a conclusion that Compound (1) is biologically active *in vivo*.

The RECIST criteria used to determine objective tumor response for target lesions, taking into account the measurement of the longest diameter for all target lesions. RECIST criteria include:

Complete Response (CR): Disappearance of all target lesions

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Table 2 shows the substantial anticancer efficacy and NK cell activity results for different subjects. The Effector/Target data shows the ratio of the subjects PBMC cells to the NK assay target cells. The pre and post dose column values show the percent of tumor cells lysed before dosing with Paclitaxel and Compound (1). Best Response indicates an evaluation of the patient's tumor: PR = at least a 30% decrease in the sum of the longest diameters as compared to baseline, while SD indicates less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline. Target Lesions indicates the percent change in targeted melanoma lesions in the subjects. NK Activity indicates the change in NK activity before and after dosing.

Table 2 shows that for patients completing the study (#1-#8) there was a substantial decrease in target lesion size for each patient. Also, 5 of the 8 patients completing the study had the best response evaluation category, at least a 30% decrease in the sum of the longest diameters compared to baseline. For NK cell activity, 8 of the 11 original patients showed an increase between pre- and post-dose

treatment, though in this example the difference was not significant according to paired t-test (p=0.06).

Table 2		% tumor cell lysis		dosing information				
Subject	Effector/ Target	pre-dose	post-dose	Paclitaxel, mg/M^2	Cmpnd (1) mg/M^2	Best Response	Target Lesions	NK activity
1	80:1	9.55	16.14	175	233	SD	-5.9%	increase
2	80:1	3.12	8.76	175	233	SD	-30%	increase
3	80:1	7.84	10.05	175	233	PR	-67%	increase
4	80:1	8.4	5.5	200	266	PR	-38%	decrease
5	80:1	7.79	30.8	175	233	PR	-34%	increase
6	80:1	3.59	7.81	200	266	PR	-44%	increase
7	80:1	0.92	7.75	175	233	SD	-24%	no change
8	80:1	10.7	14.61	175	233	PR	-62%	increase
9	80:1	7.21	10.11			NA	NA	increase
10	80:1	8	3.8			NA	NA	decrease
11	80:1	36.19	45.98			NA	NA	increase

Given the safety profile of Cohort 2, this dose level (carboplatin AUC 6, paclitaxel 200 mg/m2 and Compound (1) 266 mg/m2) was used in Phase 2.

Phase 2 included 87 patients with 44 patients in the control group that received 200 mg/m^2 paclitaxel and carboplatin AUC = 6, and 43 patients in the study group that received 200 mg/m^2 paclitaxel, carboplatin AUC = 6, and 266 mg/m^2 of Compound (1). Patients were dosed as described for phase 1. Table 3 summarized the results of the trial including overall response rate, time to progression (TTP), and survival.

Table 3	Control (N = 44)	Study Group (N = 40)*	P-Value
Response Rate, %	25.0	17.5	0.438**
Medium TTP, months	4.6 (95% C.I. = 3.1, 5.1)	3.3 (95% C.I. = 2.6, 4.1)	0.288†
Medium survival, months	8.2 (95% C.I. =5.5, 12.6)	8.2 (95% C.I. = 5.0, not estimable)	0.733†

* Three patients dropped out of the study group.

**Two-sided p-value obtained from the Fisher's exact test.

†Two-sided p-value obtained from the log-rank test.

C.I. = confidence interval (Kaplan Meier estimates)

Example 5: A 2 Stage Phase 2 Study Showing the Effect of the Disclosed Combination Therapy for Treating Advanced Metastatic Melanoma

The following study of Compound (1) and paclitaxel in patients with advanced metastatic melanoma was initiated based on the biological activity shown by the results of the above Phase I study, where the combined administration Compound (1) and paclitaxel led to dose-related Hsp70 induction.

The study included a Stage 1 initial safety assessment of the weekly dose schedule, where Compound (1) 106 mg/m2 (265 μmol/m2) and paclitaxel at 80 mg/m2 (94 μmol/m2) were administered weekly for 3 weeks out a 4 week period. The dose of Compound (1) was then escalated to 213 mg/m2 (532 μmol/m2) in combination with the paclitaxel at 80 mg/m2 (94 μmol/m2). The higher tolerated dose level was expanded to a total of 20 patients (Stage 1).

A total of 7 patients were treated in the initial safety assessment, 3 at the lower dose level and 4 at the higher. In the absence of dose-limiting toxicities in either group, the higher dose level was chosen as the dose of interest and additional patients were enrolled to complete stage 1. Adverse events seen were as expected for paclitaxel chemotherapy administration. Of 20 evaluable patients, 11 were stable at 3 months for 55% NPR.

The study will continue to Stage 2 if 7 or more patients have a response of stable disease or better, or at least 2 patients have a partial response or better. A safety assessment was performed with the first 6 patients enrolled a s the weekly dose schedule had not previously been studied in humans. The primary endpoint is non-progression rate (NPR) at 3 months and response rate. Pharmacodynamic parameters include pre and post-dose NK cell activity in blood and when possible, tumor biopsies.

Table 4 shows the significant preliminary results of anticancer efficacy and NK cell activity results when assayed 7 days after the second dose for different subjects. The Effector/Target data shows the ratio of the subjects PBMC cells to the

NK assay target cells. The pre and post dose column values show the percent of tumor cells lysed before dosing with Paclitaxel and Compound (1). Best Response indicates an evaluation of the patient's tumor: SD indicates less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline; and PD = at least a 20% increase in the sum of the longest diameters as compared to baseline. NK Activity indicates the change in NK activity before and after dosing.

Table 4 shows that for patients completing the study (#12-#20, #22), three patients had less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline, while seven patients had at least a 20% increase in the sum of the longest diameters as compared to baseline. For NK cell activity, four of the original patients showed a statistically significant increase between pre- and post-dose treatment.

Table 4		% tumor cell lysis		dosing information		Best Response	
Subject	Effector/ Target	pre-dose	post-dose	Paclitaxel, mg/M^2	Cmpnd (1) mg/M^2	cycle 2 week 4	NK activity
12	80:1	2.32	7.74	80	106	SD	increase
13	80:1	6.13	2.43	80	106	PD	decrease
14	80:1	3.83	10.77	80	213	SD	increase
15	(40:1)	3.5	10.01	80	213	PD	(increase)
16	80:1	19.71	19.78	80	213	SD	no change
17	80:1	41.61	26.52	80	213	PD	decrease
18	80:1	8.6	8.64	80	213	PD	no change
19	80:1	24.76	18.77	80	213	PD	decrease
20	80:1	16.49	5.2	80	213	PD	decrease
21	80:1	15.4	26.31	80	213	NA	increase
22	80:1	10.81	7.2	80	213	PD	decrease

The combination therapy was well-tolerated on the weekly schedule. Enrollment in the randomized portion will assess the activity of Compound (1) in combination with paclitaxel versus paclitaxel alone.

Stage 2 is planned to be a randomized 2-arm study comparing the drug combination to paclitaxel alone. The criterion for continuation to Stage 2 is >= 50% non-progression rate (NPR) at two months. A total of 78 patients are to be randomized 2:1 (combination:control). The primary endpoint is time to progression;

secondary endpoints are response rate, survival, and quality of life. Pharmacodynamic parameters will include pre- and post-dose measurements of NK cell activity in blood and, when possible, tumor biopsies.

Example 6: A Phase 2 Study Shows the Effects of the Disclosed Combination Therapy for Treating Soft Tissue Sarcomas

The following study of Compound (1) and paclitaxel in patients with soft tissue sarcomas was initiated based on the biological activity shown by the results of the above Phase I study, where the combined administration Compound (1) and paclitaxel led to dose-related Hsp70 induction.

The study is a 2 stage design, enrolling 30 patients in the first stage and adding 50 patients to total 80 in stage 2 if certain criteria are met. Major inclusion criteria are refractory or recurrent soft tissue sarcomas other than gastrointestinal stromal tumor (GIST), with evidence of recent progression. Patients are treated weekly, 3 weeks out of every 4 week cycle with 213 mg/m2 Compound (1) and 80 mg/m2 paclitaxel. For example, the compounds were administered together 3 weeks out of 4 on Days 1, 8, and 15 of a 28 day cycle as a 1 hour IV infusion. 30 Patients have been enrolled to completed accrual of Stage 1.

As used herein, "soft-tissue sarcomas" (STS) are cancers that begin in the soft tissues that support, connect, and surround various parts of the body for example, soft tissues such as muscles, fat, tendons, nerves, and blood vessels, lymph nodes, or the like. Such STSs can occur anywhere in the body, though typically about one half occur in the limbs. In various embodiments, STSs can include one or more cancers selected from liposarcoma, fibrosarcoma, malignant fibrous histiocytoma leiomyosarcoma, neurofibrosarcoma, rhabdomyosarcoma, synovial sarcoma, or the like.

Table 5 shows the preliminary results of anticancer efficacy and NK cell activity results when assayed 7 days after the second dose for different subjects. The Effector/Target data shows the ratio of the subjects PBMC cells to the NK assay target cells. The pre- and post-dose column values show the percent of tumor cells lysed before dosing with Paclitaxel and Compound (1). Best Response indicates an

evaluation of the patient's tumor: PR = at least a 30% decrease in the sum of the longest diameters as compared to baseline; SD indicates less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline; and PD = at least a 20% increase in the sum of the longest diameters as compared to baseline. NK Activity indicates the change in NK activity before and after dosing.

Table 5 shows that for patients completing the study (#23-#29, #31-33), five patients had less than 20% of an increase and less than 30% of a decrease in the sum of the longest diameters as compared to baseline, while five patients had at least a 20% increase in the sum of the longest diameters as compared to baseline. For NK cell activity, seven of the original patients showed a statistically significant increase or no change between pre- and post-dose treatment, while only four of the original patients showed a decrease statistically significant increase between pre- and post-dose treatment.

Table 5		% tumor cell lysis		dosing information		Best Response	
Subject	Effector/ Target	pre-dose	post-dose	Paclitaxel, mg/M^2	Cmpnd (1) mg/M^2	cycle 2	NK activity
23	80:1	4.28	30.48	80	213	PD	increase
24	80:1	20.74	20.04	80	213	SD	no change
25	80:1	34.28	11.86	80	213	PD	decrease
26	80:1	22.33	14.74	80	213	SD	decrease
27	80:1	10.6	22.9	80	213	SD	increase
28	80:1	17.93	28.13	80	213	SD	increase
29	80:1	6.58	17.18	80	213	PD	increase
30	(40:1)	9.88	9.91	80	213	NA	no change
31	80:1	2.62	5.46	80	213	SD	increase
32	80:1	13.03	7.41	80	213	PD	decrease
33	80:1	15.77	7.84	80	213	PD	decrease

Patients are currently being evaluated through 3 months. Adverse events seen were typical for paclitaxel administration on a similar schedule. Assessment of NK activity is ongoing. The addition of Compound (1) to the weekly paclitaxel schedule was well-tolerated.

Stage 1 accrual was completed, and a decision was made to proceed with stage 2. Patients in stage 2 of the trial received 80 mg/m2 Paclitaxel and 213 mg/m2

of Compound (1). Paclitaxel and Compound (1) were administered together 3 weeks out of 4 on Days 1, 8, and 15 of a 28 day cycle as a 1 hour IV infusion. The results of stage 1 and 2 are shown in Table 6.

Table 6

Cohort	n	Response after 3 Cycles				
		Partial Response n (%)	Stable Disease n (%)	Progressive Disease n (%)	Death without Progression n (%)	Data Missing n (%)
Stage 1	30	0	14 (47%)	12 (40%)	4 (13%)	0
Stage 2	49	2 (4%)	9 (18%)	31 (63%)	3 (6%)	4 (8%)
Overall	79	2 (3%)	23 (29%)	43 (54%)	7 (9%)	4 (5%)

Kaplan Meier estimates were as follows:

	Estimate	95% C.I.
Median Time to Progression	1.9	1.8-2.6
Non-Progression Rate at 3 months	36%	25%-46%
Non-Progression Rate at 6 months	12%	2%-22%

The confidence intervals around the time to progression and progression rate estimates overlap with outcomes for both active and inactive agents in a historical analysis of studies; however, the number of partial responses observed was not encouraging.

While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of determining a prognosis for a subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70), comprising the step of comparing natural killer (NK) cell activity in a test sample with NK cell activity in a control sample, wherein:

the control sample is taken from the subject before dosing with the agent;

the test sample is taken from the subject after dosing with the agent; and

an increase in NK cell activity in the test sample compared with the control sample is indicative of an improved prognosis.

2. The method of Claim 1, wherein the prognosis is determined for a single subject.

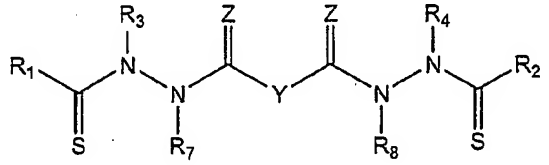
3. The method of Claim 1, wherein for each of a plurality of subjects in a population, data is collected for comparative NK cell activity between samples, dosing, and therapeutic result, further comprising analyzing the data for the population to predict a dose to achieve an improved prognosis in a subject that is representative of the subject population.

4. The method of Claim 1, wherein the NK cell activity in the control sample and the test sample is assessed by contacting each sample with target cells, and assessing a death rate for the target cells, wherein the target cell death rate corresponds to the NK cell activity.

5. The method of Claim 4, wherein the NK cell activity is assessed in one or more peripheral blood mononuclear cell (PBMC) samples isolated from the subject's blood.

6. The method of Claim 4, wherein the NK cell activity is assessed in a sample taken from a tumor in the subject.

7. The method of Claim 4, wherein the agent is a bis(thio-hydrazide) amide represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

8. The method of Claim 7, wherein the subject is human.

9. The method of Claim 8, wherein the bis(thio-hydrazide) amide is co-administered with a taxane.

10. The method of Claim 9, wherein the bis(thio-hydrazide) amide is co-administered with paclitaxel.

11. The method of Claim 10, wherein the cancer is selected from fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia; chronic leukemia; and polycythemia vera, lymphoma, multiple myeloma, Waldenstrobm's macroglobulinemia, and heavy chain disease.

12. The method of Claim 11, wherein the cancer is metastatic melanoma, non-small lung cell carcinoma, or a soft tissue sarcoma.

13. The method of Claim 10, wherein the bis(thio-hydrazide) amide is co-administered with a platinum anticancer compound.

14. The method of Claim 13, wherein the platinum anticancer compound is cisplatin; carboplatin; dexormaplatin; enloplatin; iproplatin; lobaplatin ; lomnedaplatin; ormaplatin; oxaliplatin; spiroplatin; or zeniplatin.

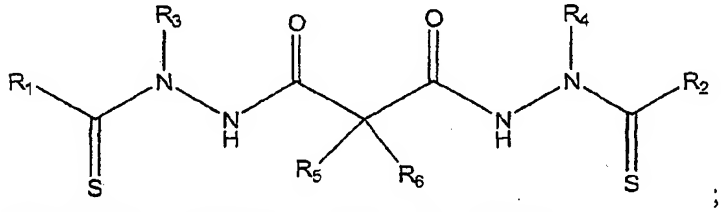
15. The method of Claim 14, wherein the platinum anticancer compound is carboplatin.

16. The method of Claim 1 wherein the test sample is taken from the subject within from about 1 hour to about 90 days after being administered the bis(thio-hydrazide) amide.

17. The method of Claim 16 wherein the test sample is taken from the subject at about 7 days after being administered a second dose of the bis(thio-hydrazide) amide.

18. The method of Claim 16 wherein the test sample is taken from the subject at about 28 days after being administered the bis(thio-hydrazide) amide.

19. The method of Claim 8, wherein the bis(thio-hydrazide) amide is represented by the following structural formula:



;

or the disodium or dipotassium salt thereof, wherein:

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 3-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-fluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-chlorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-dichlorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethylphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is ethyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is *n*-propyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both methyl;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 is methyl, and R_4 is ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclobutyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopentyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both *t*-butyl; R_5 and R_6 are both -H;

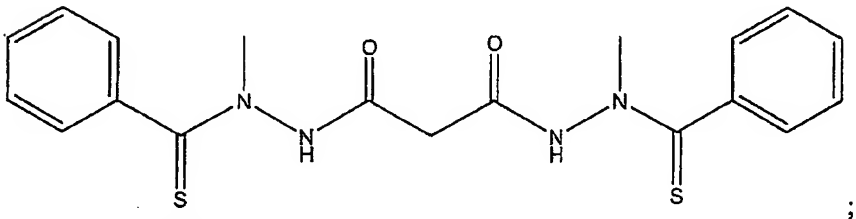
R_1 and R_2 are both methyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both *t*-butyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are ethyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H; or

R_1 and R_2 are both *n*-propyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H.

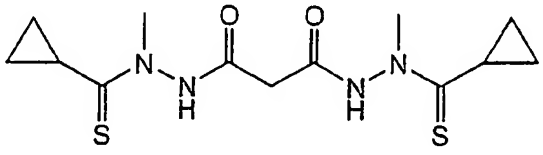
20. The method of Claim 8, wherein the bis(thio-hydrazide) amide is:



;

or the disodium or dipotassium salt thereof.

21. The method of Claim 8, wherein the bis(thio-hydrazide) amide is:



or the disodium or dipotassium salt thereof.

22. A method for optimizing dosing for at least one subject undergoing cancer therapy, wherein the dosing includes administration of an agent that activates heat shock protein 70 (Hsp70) and a taxane, comprising the steps of:

a) changing dosing of the agent and/or the taxane during therapy;

b) comparing natural killer (NK) cell activity in a control sample with NK cell activity in a test sample;

c) comparing side effects from the agent and/or taxane between the test sample and the control sample;

d) optimizing dosing of the agent and/or taxane based on the dosing in step a) in combination with the results of step b) or step c),

wherein

the test sample is taken from the subject after changing the dosing; and

the control sample is taken from the subject before changing the dosing.

23. The method of Claim 22, wherein the dosing is optimized for a single subject.

24. The method of Claim 22, wherein steps a)-c) are performed for a plurality of subjects in a population of subjects with cancer, step d) further comprising analyzing the collected results from steps a)-c) and determining a representative optimized dose based on the subject population.

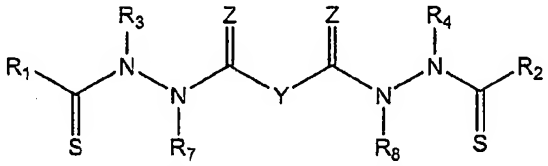
25. The method of Claim 22 further comprising repeating steps a)-c).

26. The method of Claim 18, wherein the NK cell activity in the control sample and the test sample is assessed by contacting each sample with target cells, and assessing a death rate for the target cells, wherein the target cell death rate corresponds to the NK cell activity.

27. The method of Claim 26, wherein the NK cell activity is assessed in one or more peripheral blood mononuclear cell (PBMC) samples isolated from the subject's blood.

28. The method of Claim 26, wherein the NK cell activity is assessed in a biopsy sample taken from a tumor in the subject.

29. The method of Claim 26, wherein the agent is a bis(thio-hydrazide) amide represented by the following Structural Formula:



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or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S.

30. The method of Claim 29, wherein the subject is human.

31. The method of Claim 30, wherein the taxane is paclitaxel.

32. The method of Claim 31, wherein the cancer is selected from fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia; chronic leukemia; and polycythemia vera, lymphoma, multiple myeloma, Waldenstrobm's macroglobulinemia, and heavy chain disease..

33. The method of Claim 32, wherein the cancer is metastatic melanoma, non-small lung cell carcinoma, or a soft tissue sarcomas.

34. The method of Claim 32, wherein the bis(thio-hydrazide) amide is co-administered with a platinum anticancer compound.

35. The method of Claim 34, wherein the platinum anticancer compound is cisplatin; carboplatin; dexormaplatin; enloplatin; iproplatin; lobaplatin ; lomnedaplatin; ormaplatin; oxaliplatin; spiroplatin; or zeniplatin.

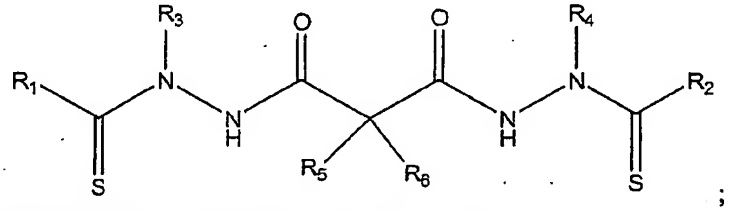
36. The method of Claim 35, wherein the platinum anticancer compound is carboplatin.

37. The method of Claim 22 wherein the test sample is taken from the subject from about 1 hour to about 90 days after being administered the bis(thio-hydrazide) amide.

38. The method of Claim 37 wherein the test sample is taken from the subject at about 7 days after being administered a second dose of the bis(thio-hydrazide) amide.

39. The method of Claim 37 wherein the test sample is taken from the subject at about 28 days after being administered the bis(thio-hydrazide) amide.

40. The method of Claim 22, wherein the bis(thio-hydrazide) amide is represented by the following structural formula:



;

or the disodium or dipotassium salt thereof, wherein:

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 3-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-fluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-chlorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-dichlorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethylphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is ethyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is *n*-propyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both methyl;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 is methyl, and R_4 is ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclobutyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopentyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both *t*-butyl; R_5 and R_6 are both -H;

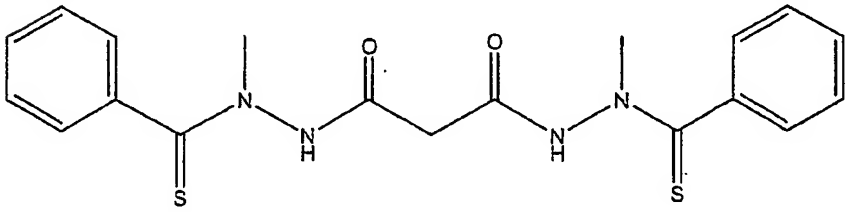
R_1 and R_2 are both methyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both *t*-butyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are ethyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H; or

R_1 and R_2 are both *n*-propyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H.

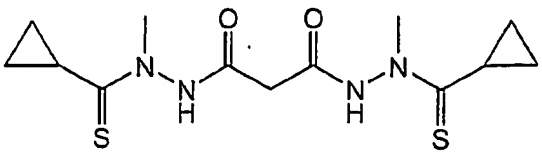
41. The method of Claim 22, wherein the bis(thio-hydrazide) amide is:



;

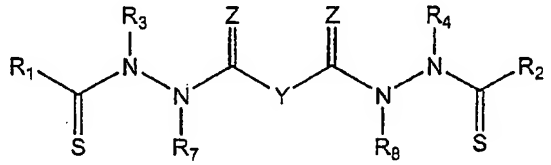
or the disodium or dipotassium salt thereof.

42. The method of Claim 22, wherein the bis(thio-hydrazide) amide is:



or the disodium or dipotassium salt thereof.

43. A method for optimizing dosing for at least one subject undergoing cancer therapy with a bis(thio-hydrazide) amide and a taxane, wherein the bis(thio-hydrazide) amide is represented by the following Structural Formula:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S,

the method comprising the steps of:

a) changing dosing of the bis(thio-hydrazide) amide and/or taxane during the cancer therapy;

b) comparing Hsp70 activity in a control sample with Hsp70 activity in a test sample;

c) comparing side effects from the bis(thio-hydrazide) amide and/or taxane at the time of the control sample with side effects from the

bis(thio-hydrazide) amide and/or taxane at the time of the test sample;

d) optimizing dosing of the bis(thio-hydrazide) amide based on the dosing in step a) in combination with the results of steps b) and c).

wherein

the test sample is taken from the subject after changing the dosing; and

the control sample is taken from the subject before changing the dosing.

44. The method of Claim 43, wherein the dosing is optimized for a single subject.

45. The method of Claim 43, wherein the dosing is optimized for a plurality of subjects in a subject population, further comprising analyzing the results for the population to predict an optimized dose for a subject that is representative of the subject population.

46. The method of Claim 43, wherein the test sample is taken from the subject from about 1 to about 48 hours after dosing.

47. The method of Claim 43, wherein the test sample is taken from the subject from about 5 to about 24 hours after dosing.

48. The method of Claim 43, wherein the test sample is taken from the subject at about 8 hours after dosing.

49. The method of Claim 46 further comprising repeating steps a)-c).

50. The method of Claim 49, wherein the Hsp70 activity is compared between samples by contacting each sample with an enzyme linked immunosorbent assay specific for Hsp70.

51. The method of Claim 50, wherein the subject is human.

52. The method of Claim 51, wherein the taxane is paclitaxel.

53. The method of Claim 52, wherein the cancer is selected from fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia; chronic leukemia; and polycythemia vera, lymphoma, multiple myeloma, Waldenstrobm's macroglobulinemia, and heavy chain disease.

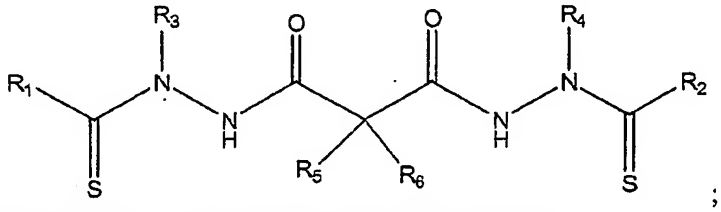
54. The method of Claim 53, wherein the cancer is metastatic melanoma, non-small lung cell carcinoma, or a soft tissue sarcoma.

55. The method of Claim 53, wherein the bis(thio-hydrazide) amide is co-administered with a platinum anticancer compound.

56. The method of Claim 55, wherein the platinum anticancer compound is cisplatin; carboplatin; dexormaplatin; enloplatin; iproplatin; lobaplatin ; lomnedaplatin; ormaplatin; oxaliplatin; spiroplatin; or zeniplatin.

57. The method of Claim 56, wherein the platinum anticancer compound is carboplatin.

58. The method of Claim 43, wherein the bis(thio-hydrazide) amide is represented by the following structural formula:



;

or the disodium or dipotassium salt thereof, wherein:

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both ethyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 4-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 3-cyanophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-fluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 4-chlorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 3-methoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,3-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-difluorophenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 2,5-dichlorophenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethylphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both phenyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2,5-dimethoxyphenyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl; R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; Y' is bond;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is methyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is ethyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 is *n*-propyl and R_6 is -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both methyl;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 and R_4 are both ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-methylcyclopropyl; R_3 is methyl, and R_4 is ethyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-methylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 2-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both 1-phenylcyclopropyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclobutyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclopentyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both cyclohexyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are both methyl; R_3 and R_4 are both *t*-butyl; R_5 and R_6 are both -H;

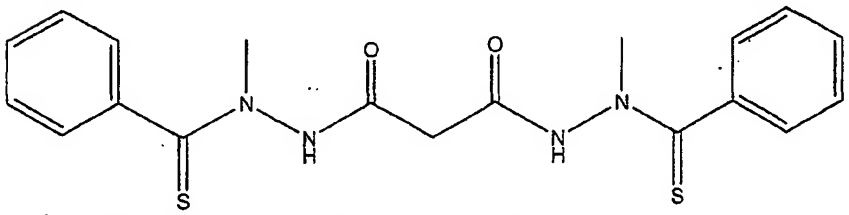
R_1 and R_2 are both methyl; R_3 and R_4 are both phenyl; R_5 and R_6 are both -H;

R_1 and R_2 are both *t*-butyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H;

R_1 and R_2 are ethyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H; or

R_1 and R_2 are both *n*-propyl; R_3 and R_4 are both methyl; R_5 and R_6 are both -H.

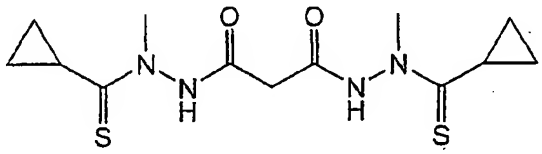
59. The method of Claim 43, wherein the bis(thio-hydrazide) amide is:



;

or the disodium or dipotassium salt thereof.

60. The method of Claim 43, wherein the bis(thio-hydrazide) amide is:



or the disodium or dipotassium salt thereof.

61. A method of dosing at least one subject undergoing cancer therapy with an agent that activates heat shock protein 70 (Hsp70), comprising administering to the subject a predicted dose based on data analysis for a representative

population, the data comprising natural killer (NK) cell activity, agent dosing, and therapeutic result.

62. The method of Claim 61, wherein the data was obtained for each member of the population by collecting:

comparative NK cell activity in a test sample with NK cell activity in a control sample wherein the control sample is taken from each member before dosing with the agent, and the test sample is taken from each member after dosing with the agent;

data for the dosing; and

a therapeutic result.

63. A method of dosing at least one subject undergoing cancer therapy, wherein the dosing includes administration of an agent that activates heat shock protein 70 (Hsp70) and a taxane, comprising administering to the subject a predicted dose based on data analysis of a representative population, the data comprising natural killer (NK) cell activity, agent/taxane dosing, and therapeutic result.

64. The method of Claim 63, wherein the data was obtained for each member of the population by:

a) changing dosing of the agent and/or the taxane during therapy;

b) comparing natural killer (NK) cell activity in a control sample with NK cell activity in a test sample;

c) comparing side effects from the agent and/or taxane between the test sample and the control sample; and

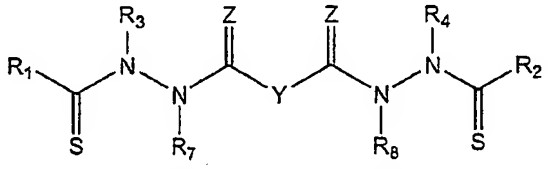
d) recording a therapeutic result of the therapy,

wherein

the test sample is taken from each member of the population after changing the dosing; and

the control sample is taken from each member of the population before changing the dosing.

65. A method for dosing at least one subject undergoing cancer therapy with a bis(thio-hydrazide) amide and a taxane, wherein the bis(thio-hydrazide) amide is represented by the following Structural Formula:



I

or a pharmaceutically acceptable salt or solvate thereof, wherein:

Y is a covalent bond or an optionally substituted straight chained hydrocarbyl group, or, Y, taken together with both >C=Z groups to which it is bonded, is an optionally substituted aromatic group;

R_1-R_4 are independently -H, an optionally substituted aliphatic group, an optionally substituted aryl group, or R_1 and R_3 taken together with the carbon and nitrogen atoms to which they are bonded, and/or R_2 and R_4 taken together with the carbon and nitrogen atoms to which they are bonded, form a non-aromatic heterocyclic ring optionally fused to an aromatic ring;

R_7-R_8 are independently -H, an optionally substituted aliphatic group, or an optionally substituted aryl group; and

Z is O or S,

the method comprising administering to the subject a predicted dose based on data analysis of a representative population, the data comprising heat shock protein 70 (Hsp70) levels, bis(thio-hydrazide) amide/taxane dosing, and therapeutic result.

66. The method of Claim 65, wherein the data was obtained for each member of the population by:

a) changing dosing of the bis(thio-hydrazide) amide and/or taxane during the cancer therapy;

b) comparing Hsp70 activity in a control sample with Hsp70 activity in a test sample;

c) comparing side effects from the bis(thio-hydrazide) amide and/or taxane at the time of the control sample with side effects from the bis(thio-hydrazide) amide and/or taxane at the time of the test sample; and

d) recording a therapeutic result,

wherein

the test sample is taken from each member of the population after changing the dosing; and

the control sample is taken from each member of the population before changing the dosing.

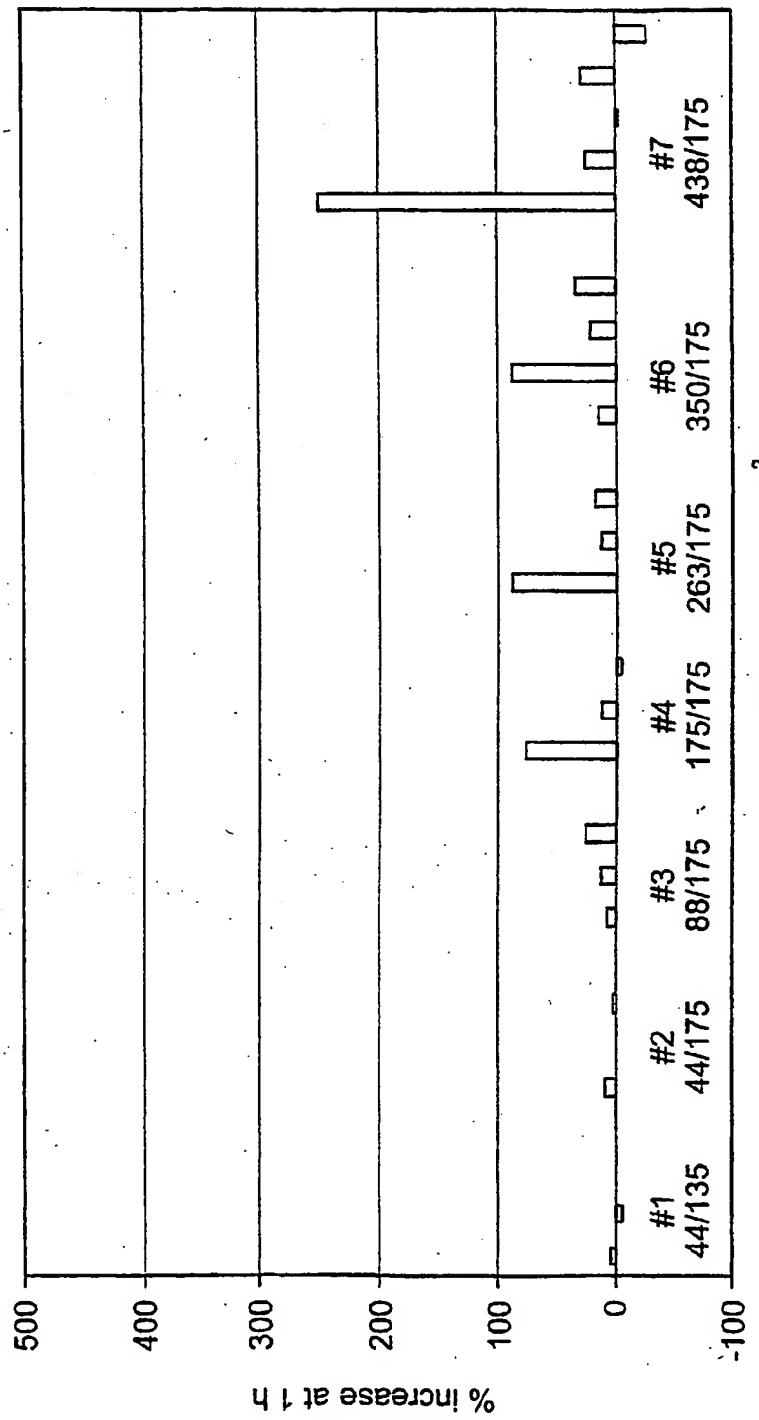

% increase at 1 h
500
400
300
200
100
0
-100
#1 44/135
#2 44/175
#3 88/175
#4 175/175
#5 263/175
#6 350/175
#7 438/175
Compound (1)/Paclitaxel (mg/m2) (1h)

FIG. 1A

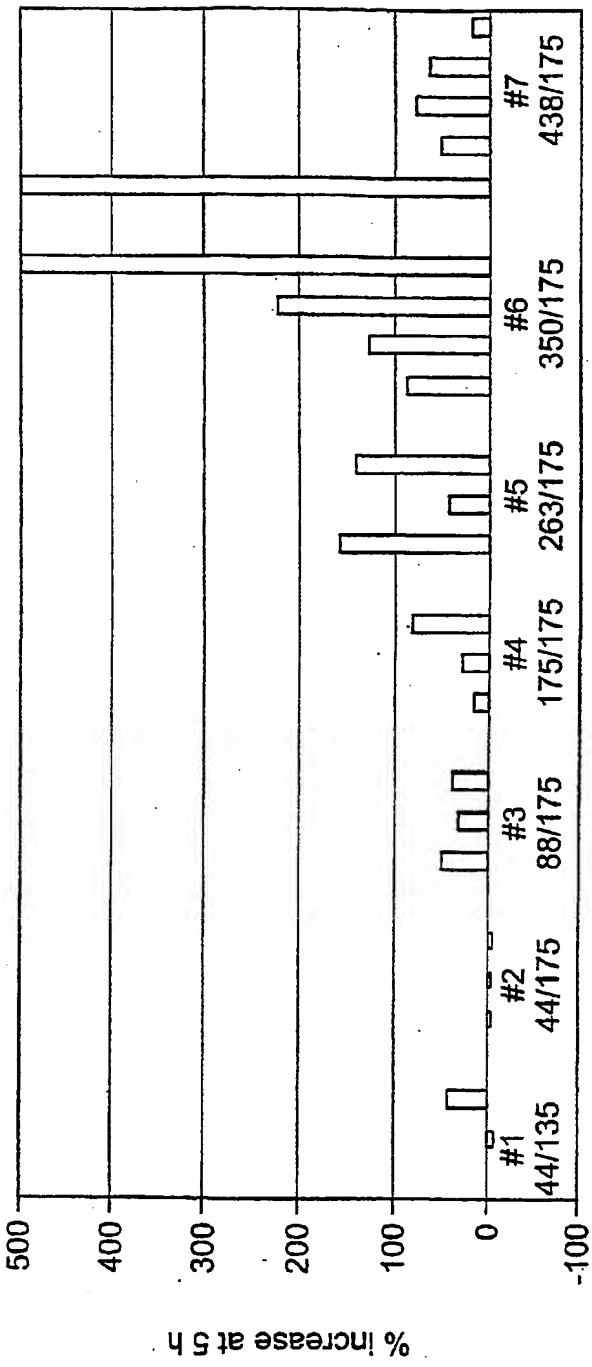

% increase at 5 h
500
400
300
200
100
0
-100
#1
44/135
#2
44/175
#3
88/175
#4
175/175
#5
263/175
#6
350/175
#7
438/175
Compound (1)/Paclitaxel (mg/m2) (5h)

FIG. 1B

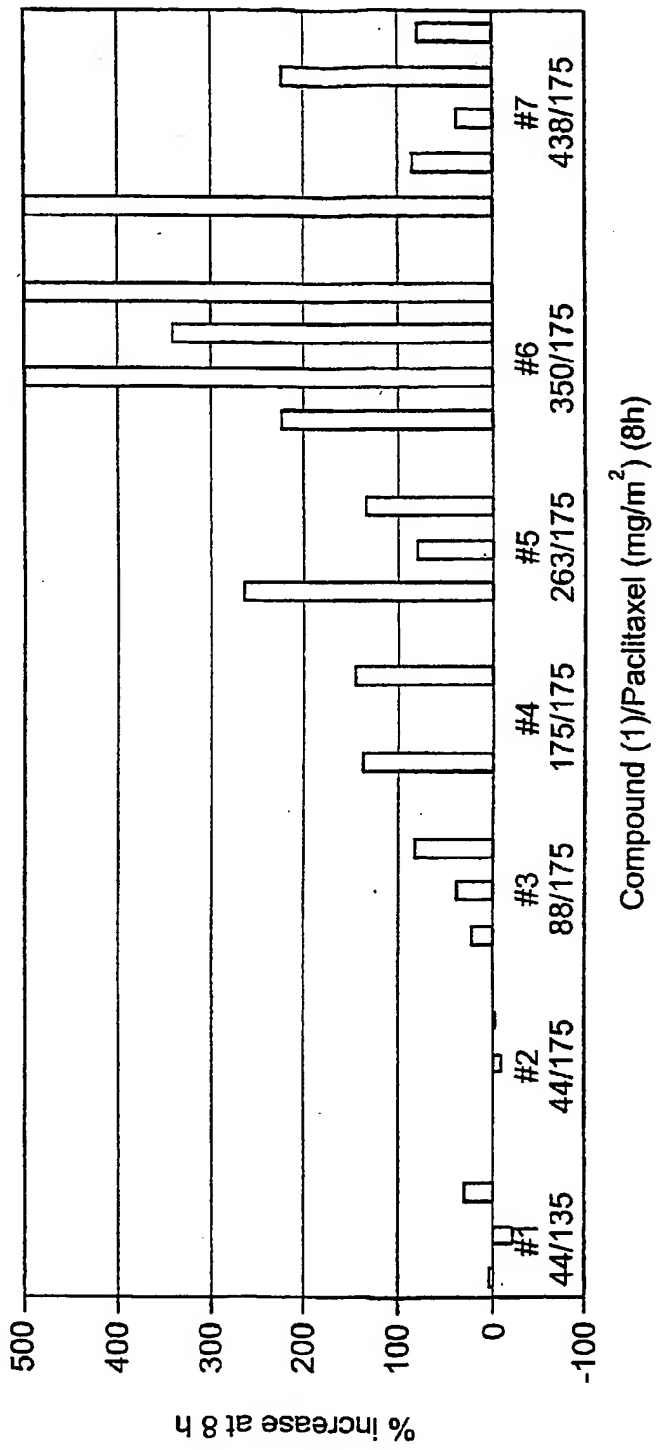

% increase at 8 h
500
400
300
200
100
0
-100
#1 44/135
#2 44/175
#3 88/175
#4 175/175
#5 263/175
#6 350/175
#7 438/175
Compound (1)/Paclitaxel (mg/m^2) (8h)

FIG. 1C

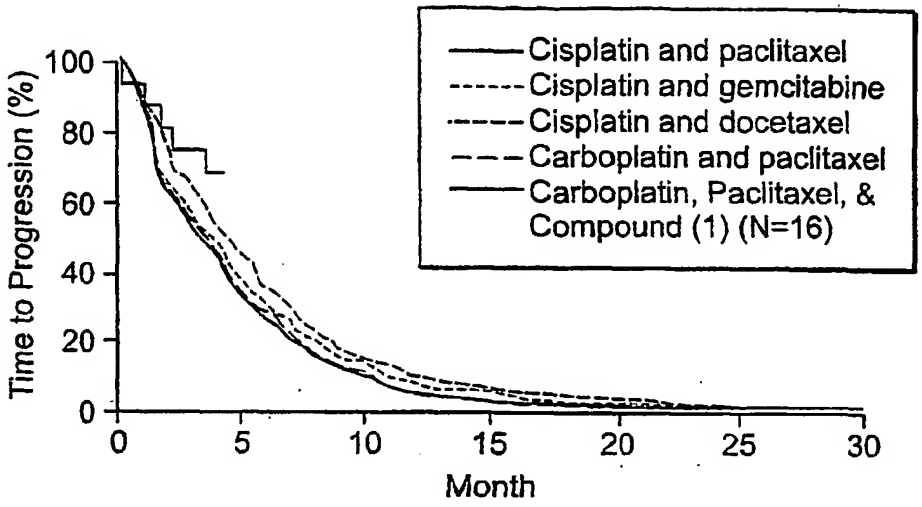

Cisplatin and paclitaxel
Cisplatin and gemcitabine
Cisplatin and docetaxel
Carboplatin and paclitaxel
Carboplatin, Paclitaxel, & Compound (1) (N=16)
Time to Progression (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Month

FIG. 2